Multicell Modeling of Developmental Phenomena using CompuCell3D

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For papers on these projects, please visit http://www.biocomplexity.indiana.edu

To download software for model building, please visit http://www.compucell3d.org

Need for Simulations

"All Models Are Wrong" (Attributed to Alan Turing).

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We all Use Models Continuously in Everything We Do—
However these Models are Usually Tacit.

Building Mathematical Models/Simulations Forces Us to
Make Our Hypotheses Explicit. Can be an
Uncomfortable Experience.

Computational Biology Goals

- To explain biological processes that result in an observed phenomena.
- To predict previously unobserved phenomena.
- To identify key generic reactions.
- To guide experiments:
  - Suggest new experiments.
  - Eliminate unneeded experiments.
  - Help interpret experiments.

Why Needed?

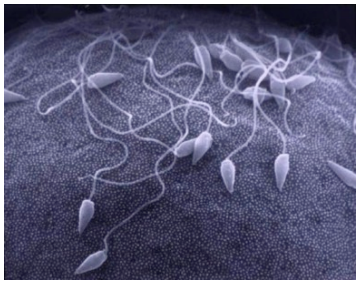
- A huge gap between level of molecular data and observed patterns.
- Most Modern Biology is descriptive rather than predictive.
- Simplify impossible complexity by forcing a hierarchy of importance – identifying key mechanisms.
- In a model know what all processes are.
- Failure of models can identify missing components or concepts.

Development in 5 Minutes

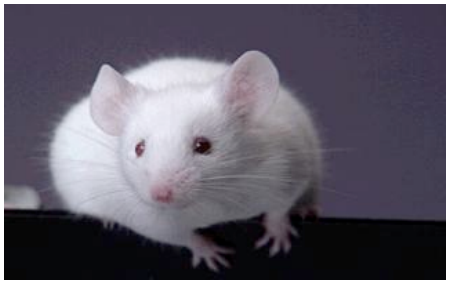
What is Development?

Biological Process by Which a

Fertilized Egg → Organism



http://www.stanford.edu/group/Urchin/LP/
[Lauren Palumbi]



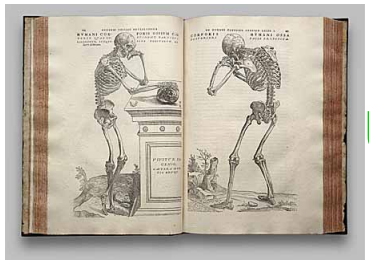
http://www.kvarkadabra.net/images/articles/Regeneracija-organov_1_original.jpg

Physical Process Which Translates

Genetic Information (Genotype)

→

http://nomadlife.org/dna.jpg



http://www.bib.sdu.dk/sund/grafik/vesalius.jpg

ucture and Behavior (Phenotype)

Biocomplexity of Development

- The classical genomic/analytic approach says "*x* happens because gene *y* is expressed"
- But how to go from expression to organism? **Why** are we not just blobs of cells expressing different genes?
- **How** does the pattern of gene expression act through physical and chemical mechanisms to result in the structures we observe? Genetics is just the beginning.
- Same mechanisms occur repeatedly in different developmental examples.
- Begin by using phenomenological descriptions. In many cases very complex pathways have fairly simple effects under conditions of interest.

Key Questions in Development

- Self Organization (Turing) vs. Positional Coding (Wolpert)?
- Genetic vs. Generic Mechanisms?
- Prepatterns (Turing) vs. Emergence (Cells Move)?
- Origin of Robustness (Twins, Plasticity and Recovery, Wound Healing, Regeneration [hydra, Axolotl])?
- Insects vs. *C. elegans* vs. vertebrates.
- Why Evolution?

Look at Development Asking What Phenomenological Behaviors Need to be Included in Models of Tissue Development

Main Processes in Development

- Cell Differentiation
- Cell Polarization
- Cell Movement
- Cell Proliferation and Death
- Cellular Secretion and Absorption

Key Questions Concerning Differentiation

- What are the types of cells in a given process?
- What signals cause cells to change types?
  - Due to diffusible substances?
  - Due to Cell-Cell Contacts?
  - Due to Cell History?
  - Due to Cell-Extracellular Matrix Contact?
- What are the thresholds for these transitions?
- How do these signals interact?
- What are the rates or probabilities of these transitions?

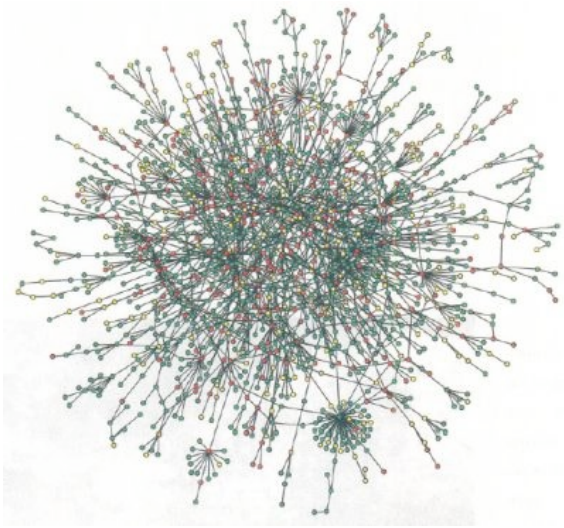
Cellular Networks

Organism	Number of Genes
Mycoplasma genitalium	482
Escherichia coli	4288
Saccharomyces cerevisiae	6275
Humans	70,000 (?)

E. Coli

350 proteins exist in concentrations of > 100 copies per cell.

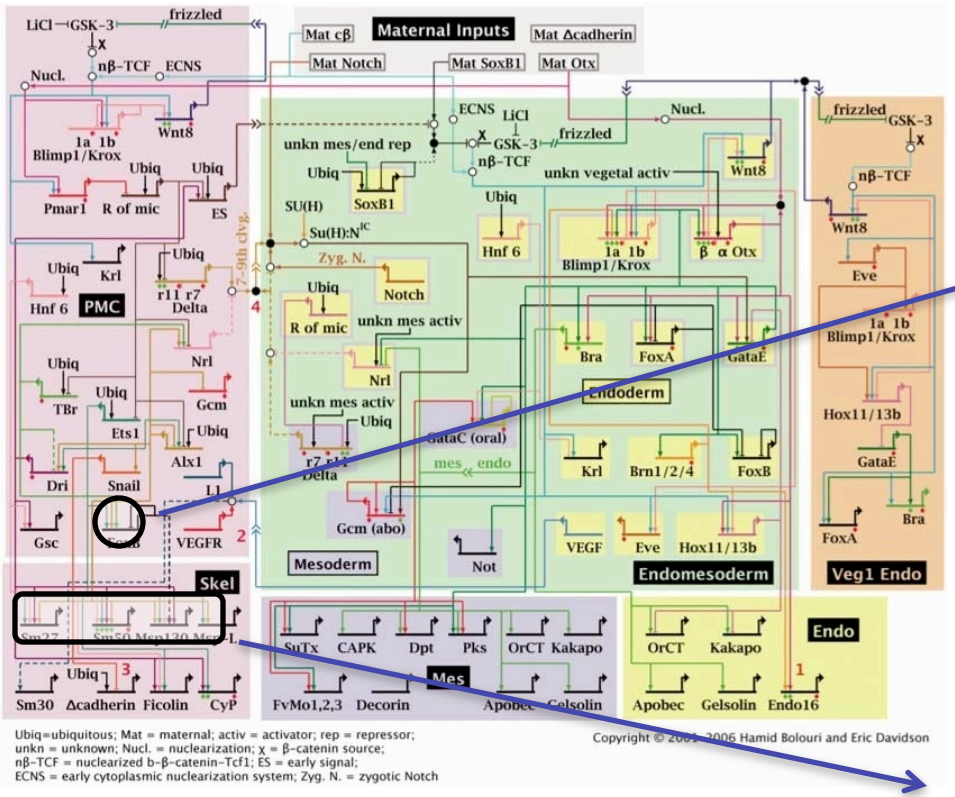
More than 80% of the proteins are present in very low amounts (< 100)

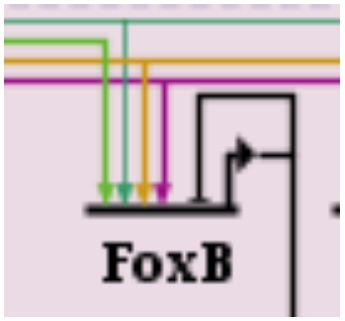


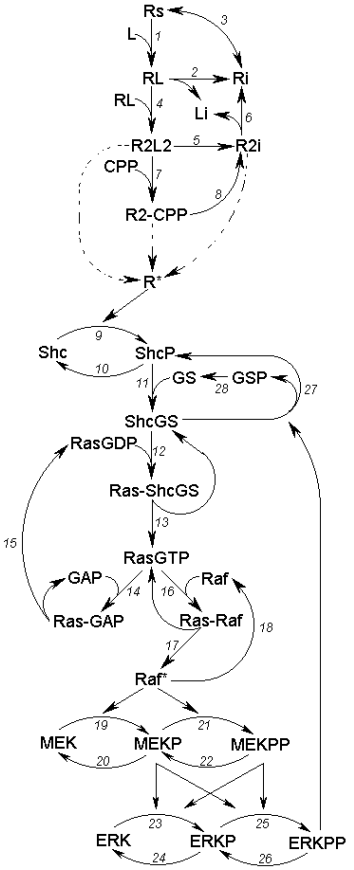
Yeast Protein-Protein Interaction Map

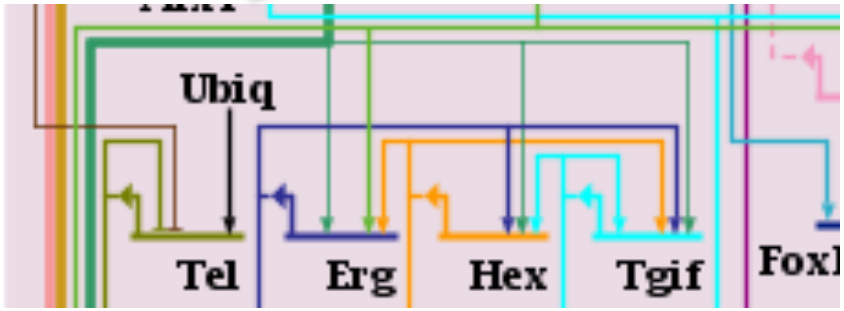
Nature **411**, 2001, H. Jeong, S. P. Mason, A.-L. Barabási, Z. N. Oltvai

Real Networks More Complex









Regulatory gene network for endomesoderm sea urchin (from Eric Davidson).

Network Physiology

Frances Brightman and David Fell

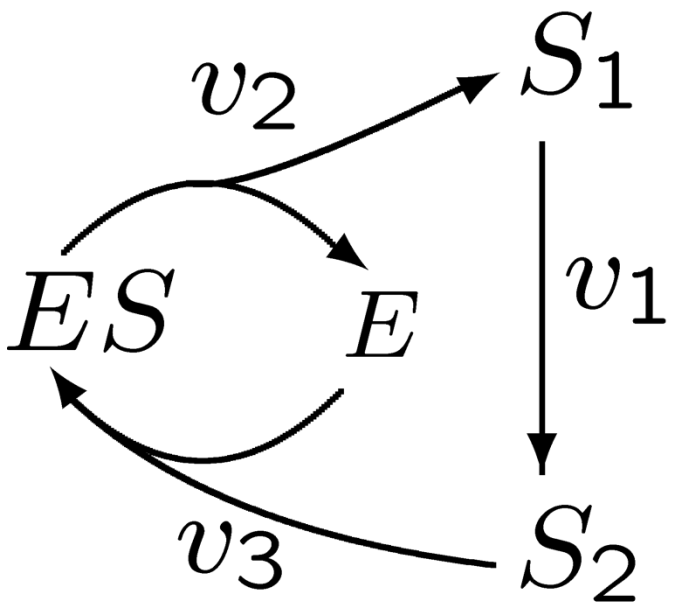
Mathematical Representations

$$\frac{dS_1}{dt} = v_2 - v_1$$

$$\frac{dS_2}{dt} = v_1 - v_3$$

$$\frac{dES}{dt} = v_3 - v_2$$

$$\frac{dE}{dt} = v_2 - v_3$$



Reaction Diffusion Equation

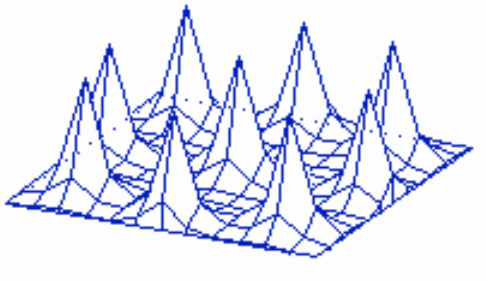
(Turing) after Cook & Murray

Two diffusing Species:Activator A; Inhibitor B

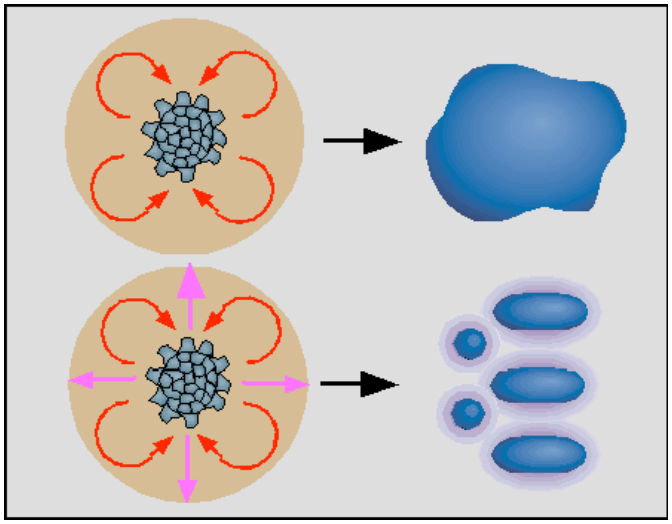
$$\frac{\partial A}{\partial t} = f(A,B) + d_A \nabla^2 A$$

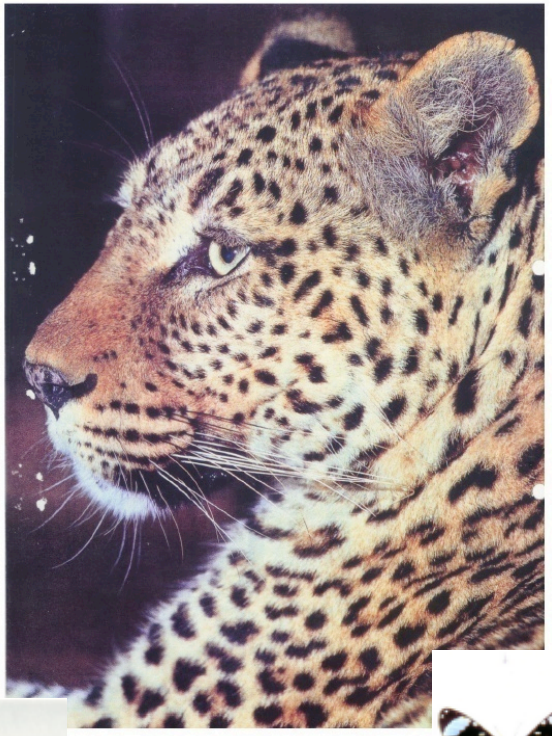
$$\frac{\partial B}{\partial t} = g(A,B) + d_B \nabla^2 B$$

$$where \frac{\partial f}{\partial A} > 0, \frac{\partial g}{\partial B} > 0, 0 < d_A < d_B$$



Activator-Inhibitor Interactions in Cartilage Pattern Formation





Philip Maini

Key Questions about Cell Classes

- What classes of cells?
- Do cells change class (e.g. Epithelia→Mesenchymal)?
- Under what signals?
- How do cells change shape?
- How strongly do cells of one type adhere to cells of another type?
- How strongly do cells of a given type adhere to ECM?
- How does cell adhesion change in time?

Cell Growth and Death

- What signals cause cells to grow?
- What signals cause cells to die?

Multicell Models

- Distinguish two questions:
  - How does genetics drive cell phenomenology?
  - How does cell phenomenology drive tissue-level patterning?
- Most mammalian cells are fairly limited in their behaviors. They can:
  - Grow,
  - Divide,
  - Change Shape,
  - Move Spontaneously
  - Move in Response to External Cues,
  - Stick,
  - Absorb,
  - Secrete,
  - Exert Forces
  - Change their local surface properties
  - (Send Electrical Signals)

  A long list, but not compared to ~10^{10} gene-product interactions.
- Many cells have relatively simple phenomenological behaviors most of the time.

Microsoft Word is NOT a Novel

(Though it may be worth writing a novel about its inconveniences)

- It IS a Tool for writing.
- Life would be even worse if you had to rewrite the word processor every time you wanted to write a letter.
- (The Novel is the Hard Part).
- Similar tools exist in Molecular Dynamics, Finite Element simulations…
- NOT for Multiscale Multi-Cell modeling.

CompuCell3D

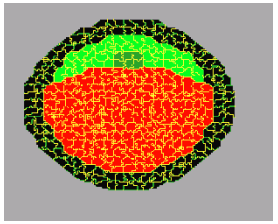
- **Open-Source, Platform-Independent Simulation Environment which allows Complex Simulation Specification and Execution using a Standard Language.**
- **Makes Simulation Development Fast, Extensible, Sharable, Easy to Validate and Publish.**
- **Usable by Nonspecialists.**
- **If you are Reading Your E-mail: Try Going to www.compucell3d.org and Installing it on your Computer Now! (You may need to Install Python 2.5 First www.Python.org).**

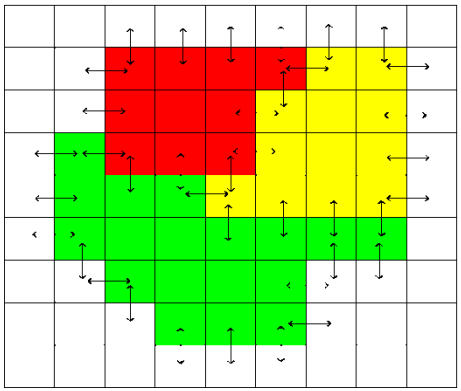
GGH Model Components

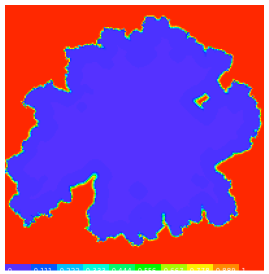
- Objects/Representations
- Object Properties/Interactions
- Dynamics
- ‘Tweaks’
- Initial and Boundary Conditions

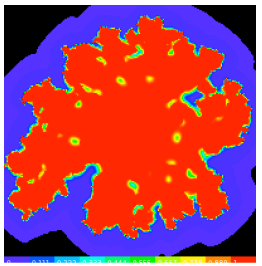
GGH Objects/Representation

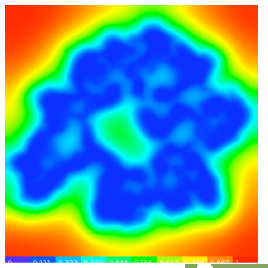
- Fundamental Entities are **Cells** and **Generalized Cells** (*e.g.* mesenchymal cells, epithelial cells, ECM, medium…), represented on the primary **Cell Lattice** (usually a square lattice with third or fourth neighbor interactions). We denote lattice position by $\vec{i}$
- Cells have **Internal States** and **Types** which describe their properties.
- Have **External Chemical Fields** represented on **Auxiliary Lattices** with same geometry as the Cell Lattice.









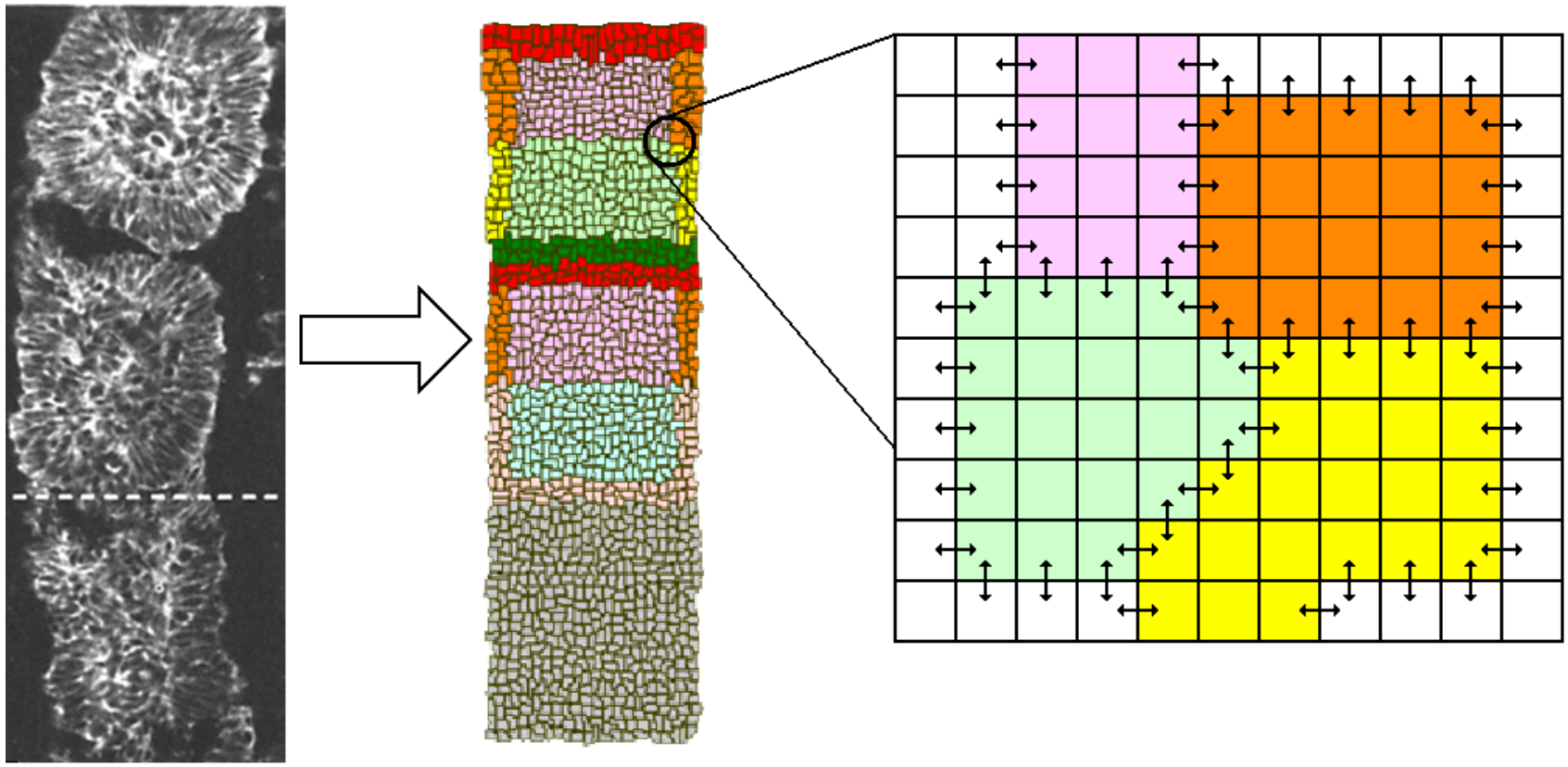


ECM MDE nutrien

GGH Cell Properties/Interactions

- Most biological properties of Cells and their interactions with each other and with Fields are Encapsulated in the Effective Energy, H.
- H is the sum of many separate terms.
- Each term in H encapsulates a single biological mechanism.
- Cell Properties described as **Constraints**.

GGH Model



$$E = \sum_{x,x'} J_{\tau(\sigma(x)),\tau(\sigma(x'))}(1-\delta_{\tau(\sigma(x)),\tau(\sigma(x'))}) + \lambda_s(s_\sigma - S_\sigma)^2 + \lambda_v(v_\sigma - V_\sigma)^2$$

$$\begin{aligned} P(\Delta E) &= 1, \ \Delta E \leq 0 \\ P(\Delta E) &= e^{-\Delta E/kT}, \ \Delta E > 0 \end{aligned}$$

Available Mechanisms in CompuCell3D

- Control of Cell Differentiation, Signaling, Growth, … via Coupled ODEs
- Reaction-Diffusion Equations (PDEs)
- Cell Adhesion
- Membrane Areas
- Mitosis
- Apoptosis
- Secretion and Absorption of Materials
- Viscosity
- Chemotaxis
- Haptotaxis
- Rigid-Body Motion
- Inertial/Persistent Motion
- Explicit External Forces
- Gravity
- Compartmental Cell Models
- Cell Polarity
- Complex Cell Shapes and Cell-Shape Changes.
- …..

Building A Model

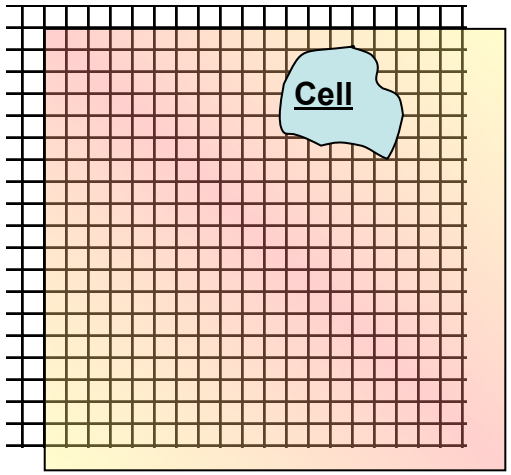
- Define Objects (Cells, Cell Types and Fields).
- Define Energy Terms.
- Define Initial Conditions.
- Pick Parameter Values (Hard, but some rules of thumb).

- Run…

CC3DML

The most commonly needed functions are predefined in CC3D and are specified using a specific eXtended Markup Language (XML).

Define Cell Lattice and Simulation Parameters



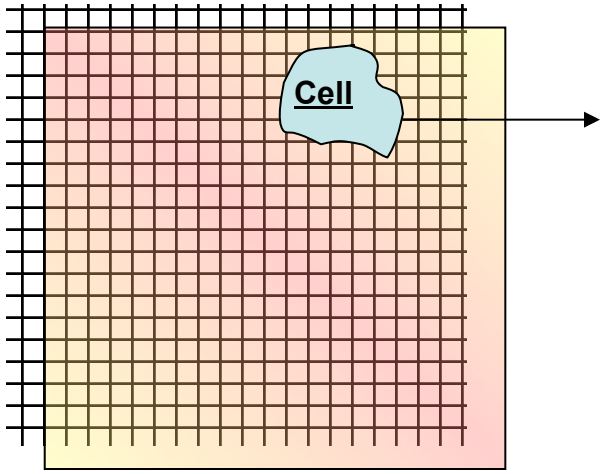

```
< CompuCell3D>
 <Potts>
   <Dimensions x="100" y="100" z="1"/
>
   <Steps>10</Steps>
   <Temperature>2</Temperature>
   <Flip2DimRatio>1</Flip2DimRatio>
 </Potts>

…

</CompuCell3D>
```

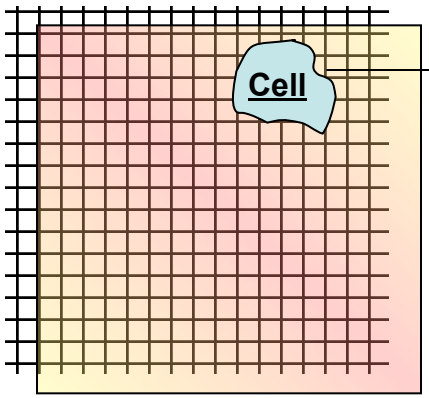
Define Cell Types Used in the Simulation

Each CC3DML file must list all Cell Types that will used in the simulation




```
<Plugin Name="CellType">
   <CellType TypeName="Medium"
TypeId="0"/>
   <CellType TypeName=“Light" TypeId="1"/>
   <CellType TypeName=“Dark" ="2"/>
 </Plugin>
```

Define Energy Terms of the Effective Energy and their Parameters



Volume

volume
volumeEnergy(cell)

```
<Plugin Name="Volume">
<TargetVolume>25</TargetVolume>
<LambdaVolume>1.0</LambdaVolume>
</Plugin>
```

Surface

area
surfaceEnergy(cell)

```
<Plugin Name="Surface">
 <TargetSurface>21</TargetSurface>
 <LambdaSurface>0.5</LambdaSurface>
</Plugin>
```

Contact

contactEnergy(
cell1, cell2)

```
<Plugin Name="Contact">
  <Energy Type1="Medium" Type2="Medium">0
  </Energy>
  <Energy Type1="Light" Type2="Medium">0
  </Energy>
  <Energy Type1="Dark" Type2="Medium">0.1
  </Energy>
  <Energy Type1="Light" Type2="Light">0.5
  </Energy>
  <Energy Type1="Dark" Type2="Dark">3.0
  </Energy>
  <Energy Type1="Light" Type2="Dark">0.5
  </Energy>
</Plugin>
```

Subcellular Reaction Networks and Supercellular PDEs

- Use your favorite Subcellular model package (SBW, Fortran, C++, Mathematica, Matlab,…)
- Current Version: Use standard Python glue files to run network inside each CC3D cell.
- Beta Test Version allows evaluation of arbitrary ODEs and PDEs using CC3D's solvers (Production release November).
- Alpha Test Version provides substantial integrated interoperability between SBW and CC3D (Beta release by end of year).

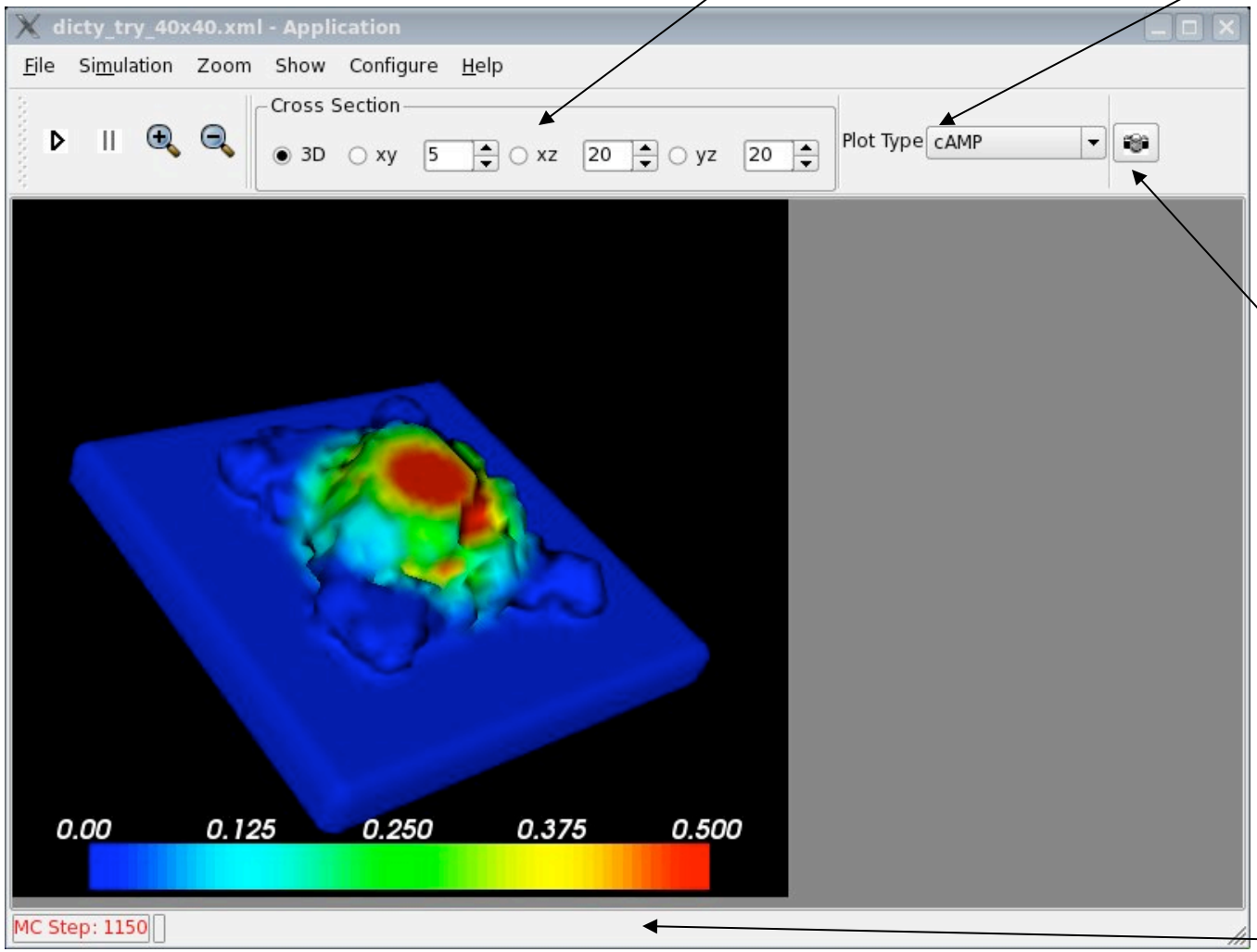
Python Scripting

Simple example to print cell id, cell type and cell volume for every cell in the simulation (user code in blue, template code in grey).

```
class InfoPrinterSteppable(SteppablePy):
   def __init__(self,_simulator,_frequency=10):
      SteppablePy.__init__(self,_frequency)
      self.simulator=_simulator
      self.inventory=self.simulator.getPotts().getCellInventory()
      self.cellList=CellList(self.inventory)
   def start(self):
      print "This function is called once before simulation“\
   def step(self,mcs):
      print "This function is called every 10 MCS“
      for cell in self.cellList:
         print "CELL ID=",cell.id, " CELL TYPE=",cell.type," volume=",cell.volume
```

Running the Simulation

Steering bar allows users to start or pause the simulation, zoom in , zoom out, to switch between **2D and 3D** visualization, change **view modes** (cell field, pressure field , chemical concentration field, velocity field etc..)



Player can output multiple views during single simulation run – **Add Screenshot** function

Information bar

Tumors

Biomedical Background

- **Issue:**Most Tumors are Only Dangerous when:
  - They become **neovascularized** (induce growth of new blood vessels to provide nutrients).
  - They **metastasize** (their cells migrate--usually via the blood stream) to form numerous secondary tumors.

- **Idea:** ~20 years ago—use drugs to block neoangiogenesis (*e.g.* Avastin).

- **Result:** Sometimes it works, sometimes the antiangiogenic drug **induces metastasis** (makes things **much worse**).

Start with Anderson Tumor Model

Cell Types:

- normal (Motile, Adhere Strongly, chemorepelled by ECM, divide, consume nutrients, secrete MDE, mutate).
- quiescent (Induced by pressure, Motile, Adhere Strongly, chemorepelled by ECM, consume nutrient, do not divide).
- mutated (Motile, Adhere Weakly, chemorepelled by ECM, divide, consume nutrients, secrete MDE).
- necrotic (Passive, gradually shrink).

Fields:

- nutrient (aggregates Oxygen if needed, glucose, *etc*…).
- surrounding tissue (ECM) (aggregates non-cellular material and normal cells, *etc*…).
- matrix degrading enzyme (MDE) (aggregates lactic acid and MMPs).

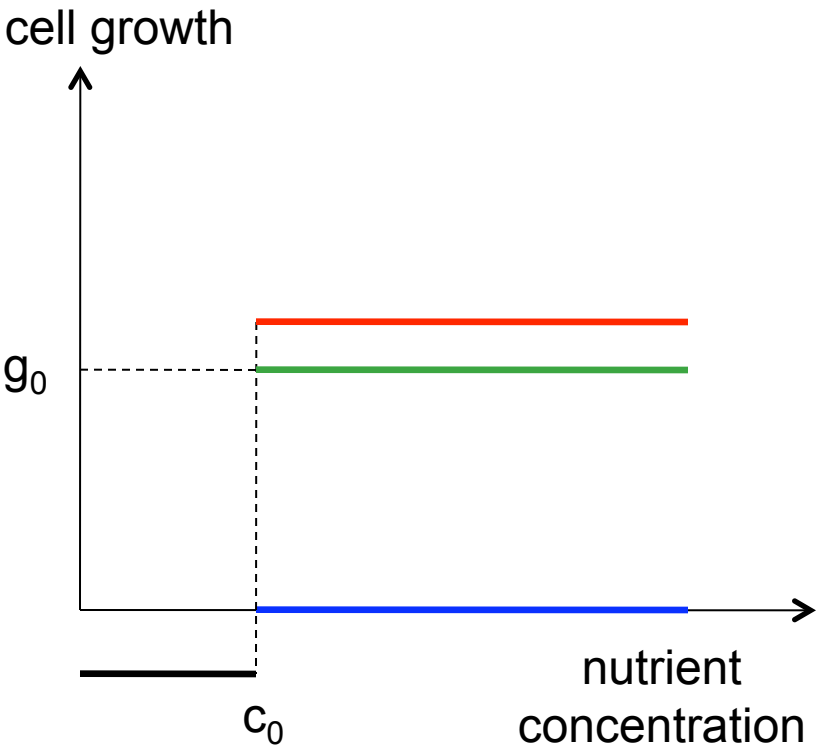
Reaction-diffusion equations for Fields:

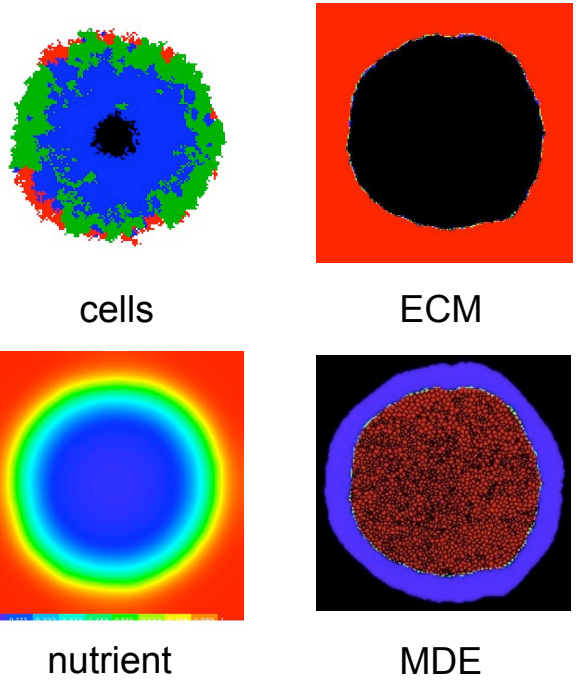
Nutrient: concentration change = diffusion + production by ECM – uptake by tumor cells – decay

MDE: concentration change = diffusion + production by cells – decay

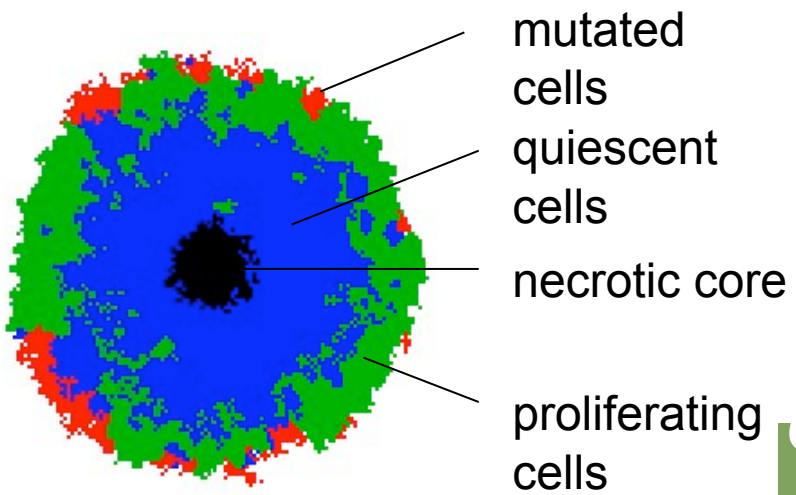
ECM: concentration change = – degradation by MDE

CONSTANT GROWTH RATE ABOVE THRESHOLD

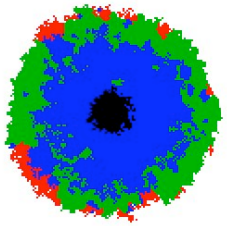




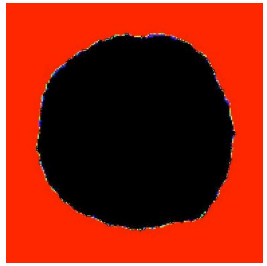
Benign Tumor
Sufficient supply of nutrients



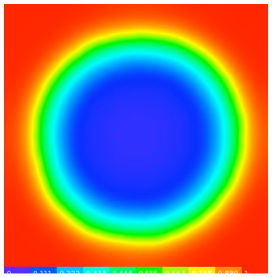
CONSTANT GROWTH RATE ABOVE THRESHOLD



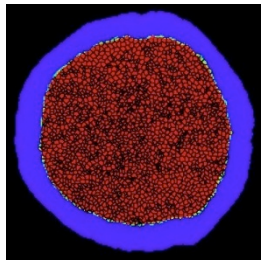
cells



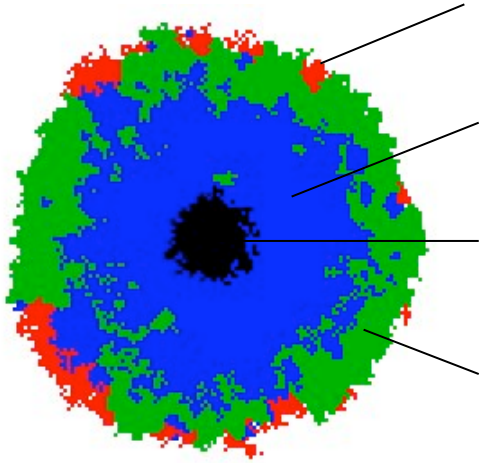
ECM



nutrient



MDE



mutated cells

quiescent cells

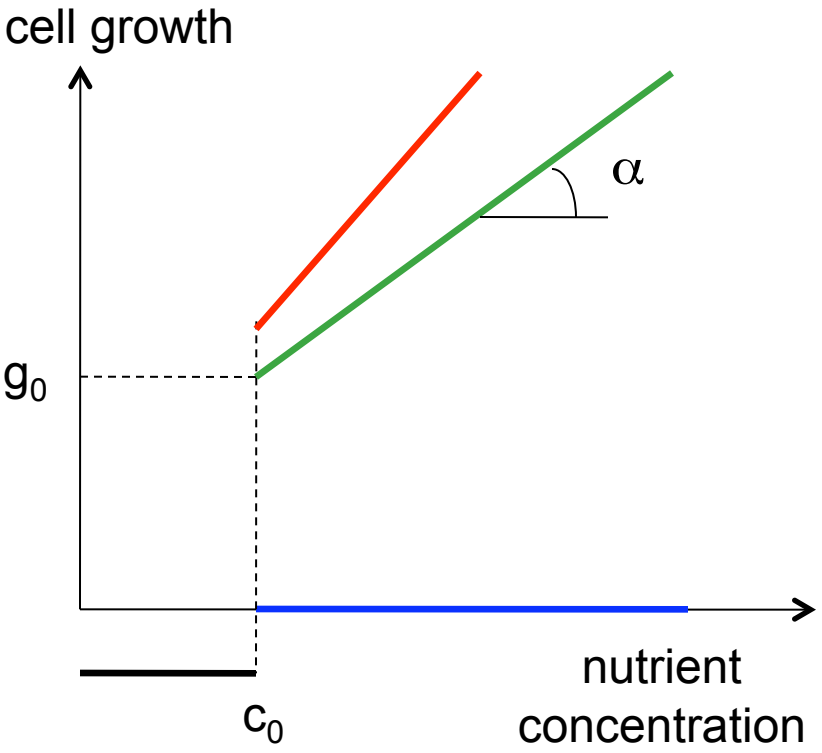
necrotic core

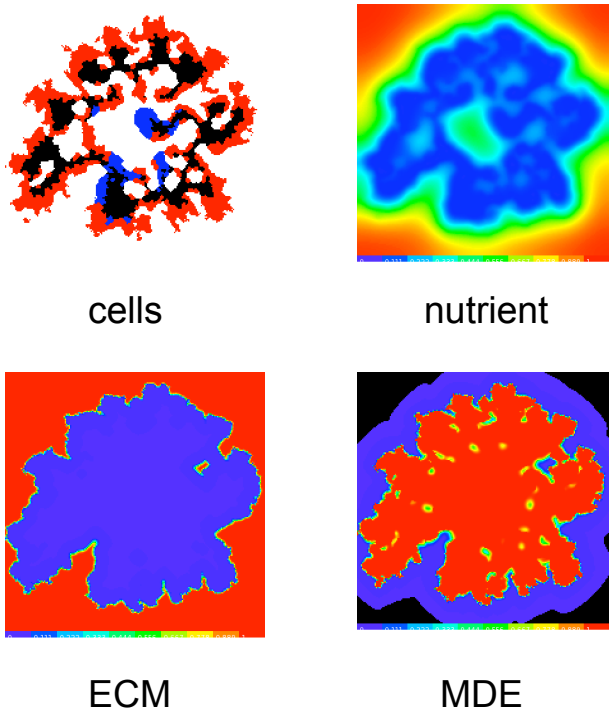
proliferating cells

Benign Tumor

Sufficient supply of nutrients

GROWTH RATE PROPORTIONAL TO NUTRIENT CONCENTRATION ABOVE THRESHOLD

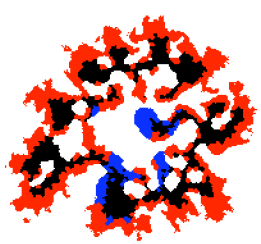




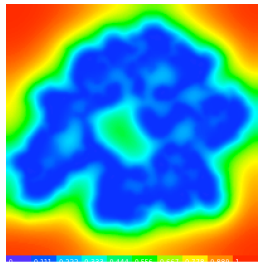
Malignant Tumor

Sensitivity of growth to nutrient supply leads to fingering instabilities (and possibly metastasis)

GROWTH RATE PROPORTIONAL TO NUTRIENT CONCENTRATION ABOVE THRESHOLD

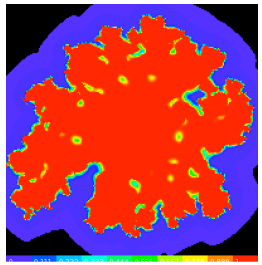


cells



nutrient

ECM



MDE

Malignant Tumor

Sensitivity of growth to nutrient supply leads to fingering instabilities (and possibly metastasis)

Suggests that Growth rate/properties of cells can determine invasiveness. Tissue inhomogeneity NOT needed.

Now simplify much further:

One cell type.

One diffusing field (nutrient).

Two parameters:

G —The Dimensionless ratio between nutrient diffusion and growth rate (determines if growing periphery of tumor is nutrient limited).

γ —The effective tumor surface tension (aggregates many things but effectively ratio between tumor-cell-tumor-cell binding and tumor-cell-ECM binding, *i.e*. cadherins/integrins. $\uparrow$Integrin, $\downarrow$cadherin $\Rightarrow \downarrow \gamma$.

	G=4	G=8	G=12	G=16	G=20	G=24
γ=6	.	.	.	.	.	.
γ=4	.	.	.	.	.	.
γ=2	.	.	.	.	.	.
γ=0	.	.	.	.	.	.

Result and Sample Clinical Deduction

1) Competition for nutrients as measured by *G*, controls tumor morphology (spherical benign vs. fingering malignant). (Agrees with *in vitro* experiments as reported in P. Macklin, J. Lowengrub, *J. Theor. Biol.* (2007)).

2) For Fixed *G*, smaller γ are more invasive.

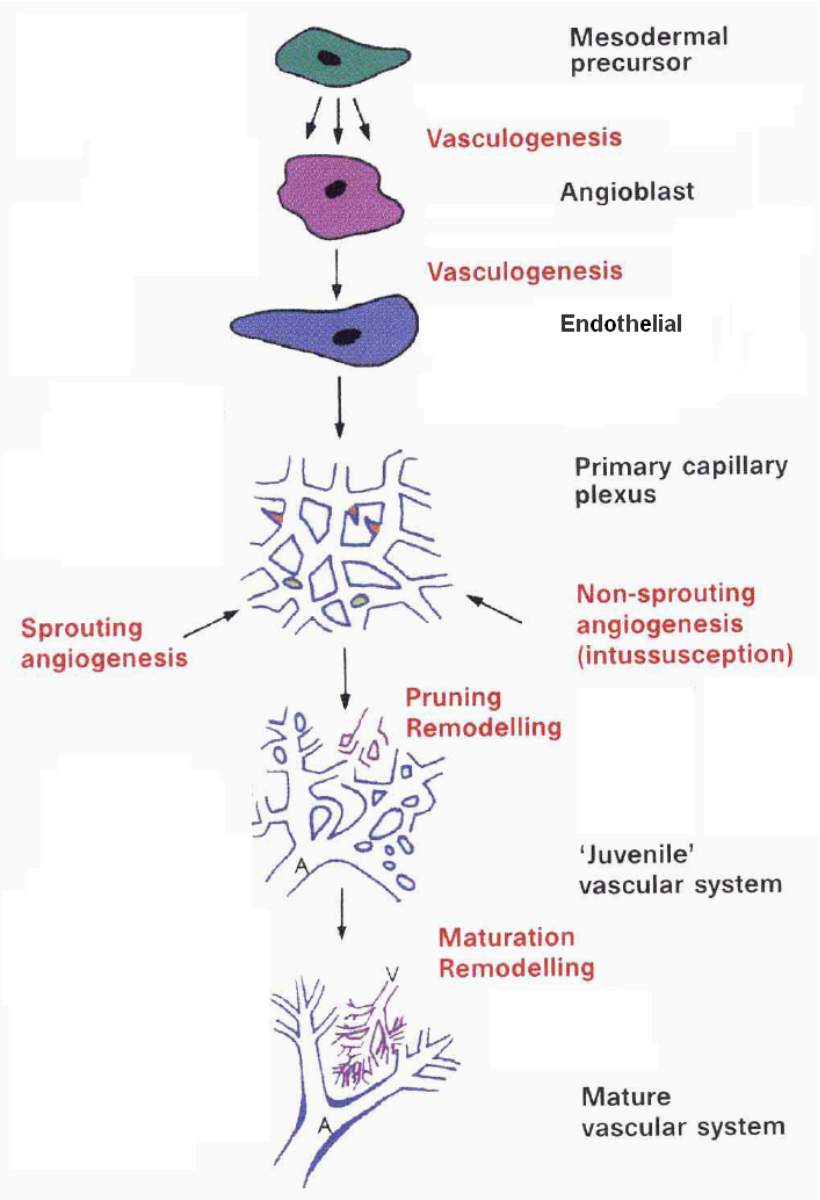
3) Small γ tumors are more sensitive to nutrient limitation than large-γ tumors.

4) Can INFER G and γ from Tumor Morphology.

Implication: If Tumor has morphology in high *G*, γ range, then antiangiogeneic therapy may be helpful. If in low *G*, γ range, antiangiogenic therapy is likely to promote metastasis.

Now Add Vasculogenesis

- Vasculogenesis
  - The formation of early vascular plexus from in situ differentiated **Endothelial Cells** (***ECs***)
- Angiogenesis
  - The formation of new blood vessels from pre-existing ones
    - Sprouting Angiogenesis
    - Non-sprouting Angiogenesis (**Intussusceptive angiogenesis**)



Werner Risau, *Nature* **386**, 671 - 674 (1997)

Vascular Development

Biological System

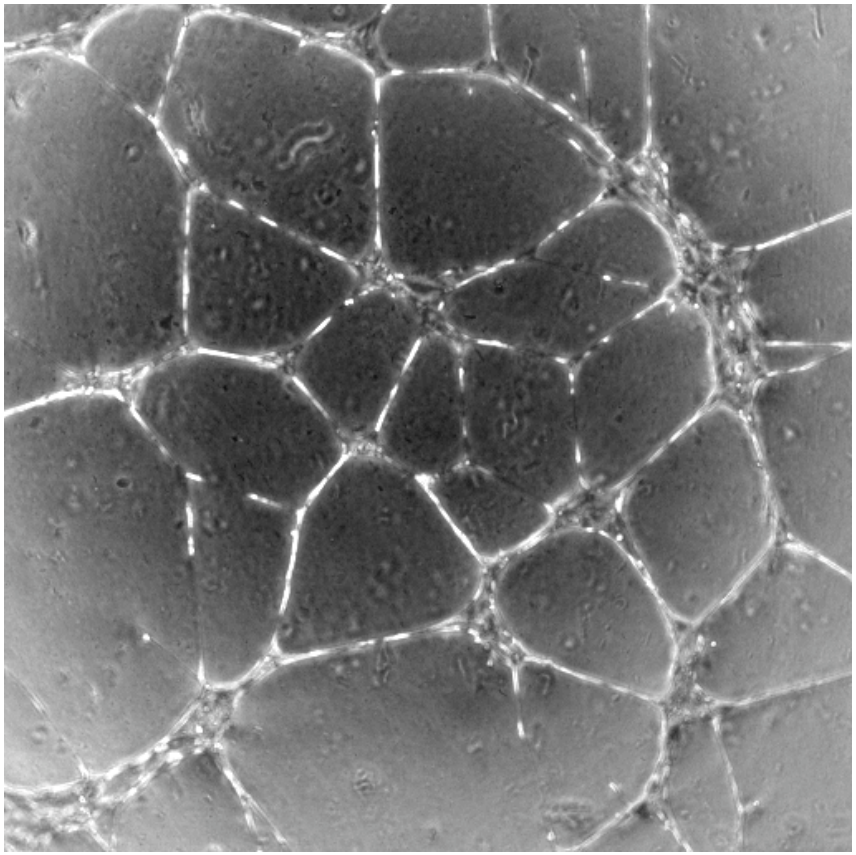
- Umbilical Vein Endothelial Cells (HUVECs) on Matrigel

Can We Reproduce *in vitro* vasclar Patterning?

Can We determine the chemoattractant?

Can we Define the roles of Contact inhibition and Cell Elongation?

Can the Same Model reproduce Both Vasculogenesis (random initial conditions) and Angiogenesis (Sprouting)?



Movie 1

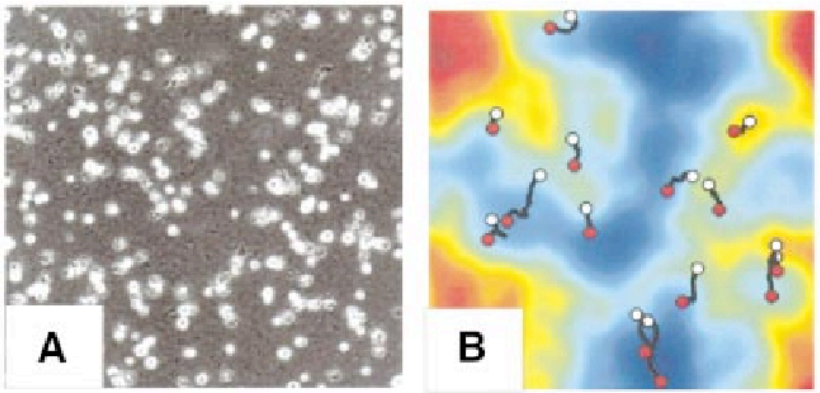
Movie 1: D. Ambrosi et al., Phys. Rev. Letters **90**, 118101

Vasculogenesis based on

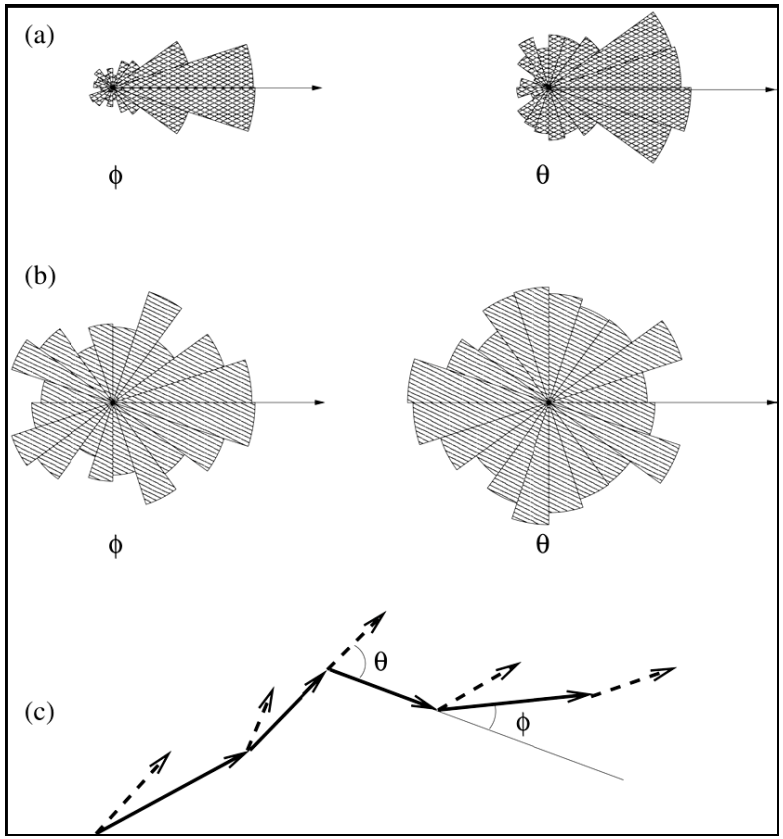
Chemotaxis Hypothesis

(Gamba *et al.* 2003; Serini *et al.*, 2003)

- Cells migrate to higher concentrations of cells
- Saturation of **VEGF-A gradients** inhibits directional cell migration
- ECs produce VEGF-A during first hour of vascular development



Red circles: starting point. White circles: arrival point.



Solid arrows represent cell displacements; dashed arrows represent chemoattractant Gradients.

Vascular Development

Two Cell Types: Vascular Endothelial Cells (ECs), Medium
One Field: Vascular Endothelial Growth Factor A (VEGF-A)

$$H = \sum_{\substack{\vec{i},\vec{i}' \\ \text{neighbors}}} J\left(\tau(\sigma(\vec{i})),\tau(\sigma(\vec{i}'))\right)\left\{1-\delta\left(\sigma(\vec{i}),\sigma(\vec{i}')\right)\right\} + \sum_{\substack{\vec{i} \\ \text{restricted to Cell} \\ \text{sites next to Medium}}} \mu\left(\tau\left(\sigma\left(\vec{i}\right)\right)\right)\frac{C\left(\vec{i}\right)}{\gamma C\left(\vec{i}\right)+1}$$

$$+\sum_{\sigma}\lambda_{\text{volume}}\left(V(\sigma)-V_{\text{target}}\right)^2+\lambda_{\text{surface}}(\sigma)\left(S(\sigma)-S_{\text{target}}(\sigma)\right)^2$$

Surface tension Between Cells set to 0 (No Adhesion).

Cells are floppy.

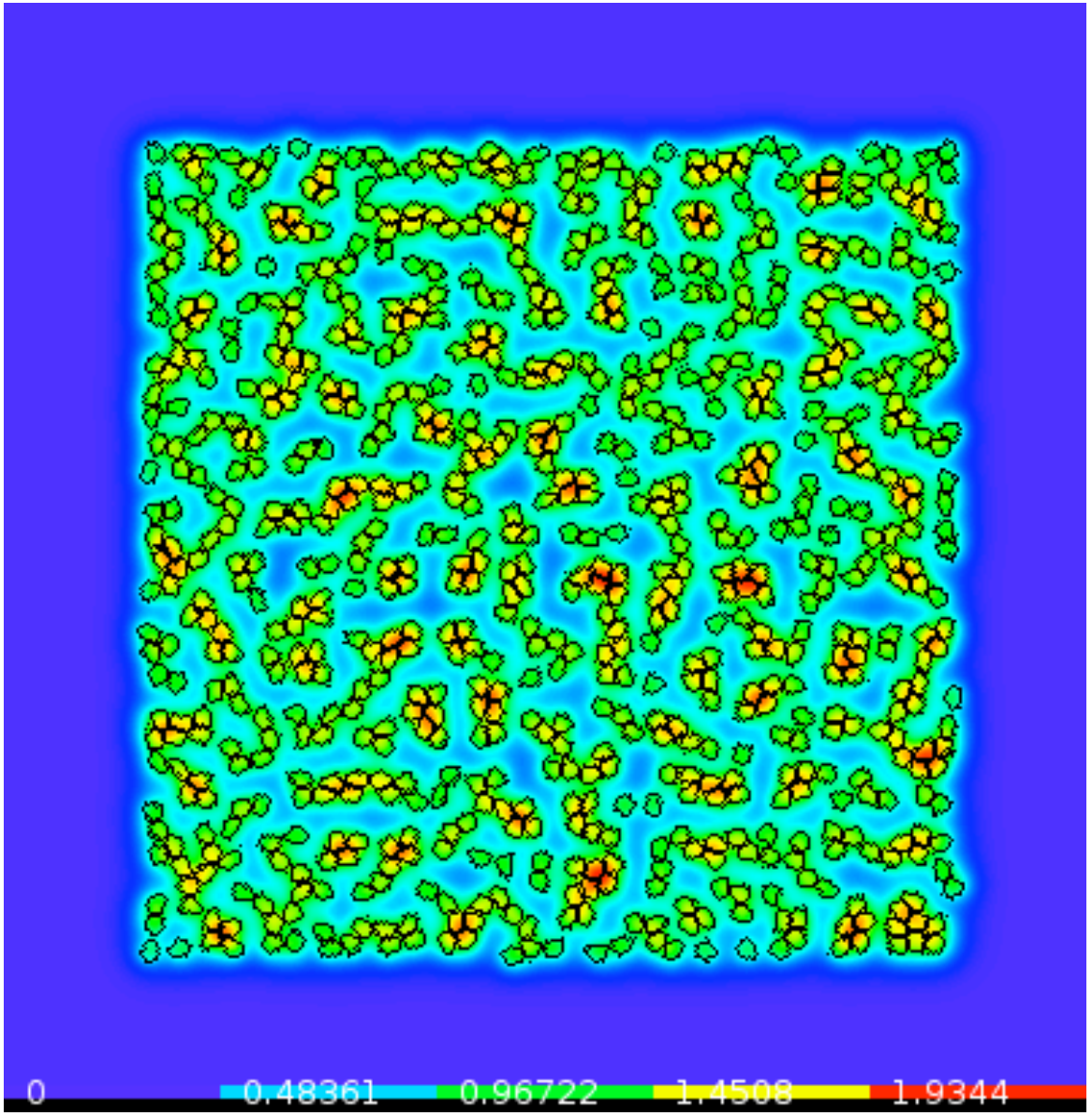
Cells secrete and chemotax (with Contact Inhibition) to a diffusible chemical field, which decays in the external environment (autocrine signaling)

$$\frac{\partial C\left(\vec{i}\right)}{\partial t} = D_c\nabla^2 C\left(\vec{i}\right) - \gamma_c C\left(\vec{i}\right) + S_c\,\delta\left(\tau\left(\sigma\left(\vec{i}\right),EC\right)\right)$$

Random blob Initial Conditions or

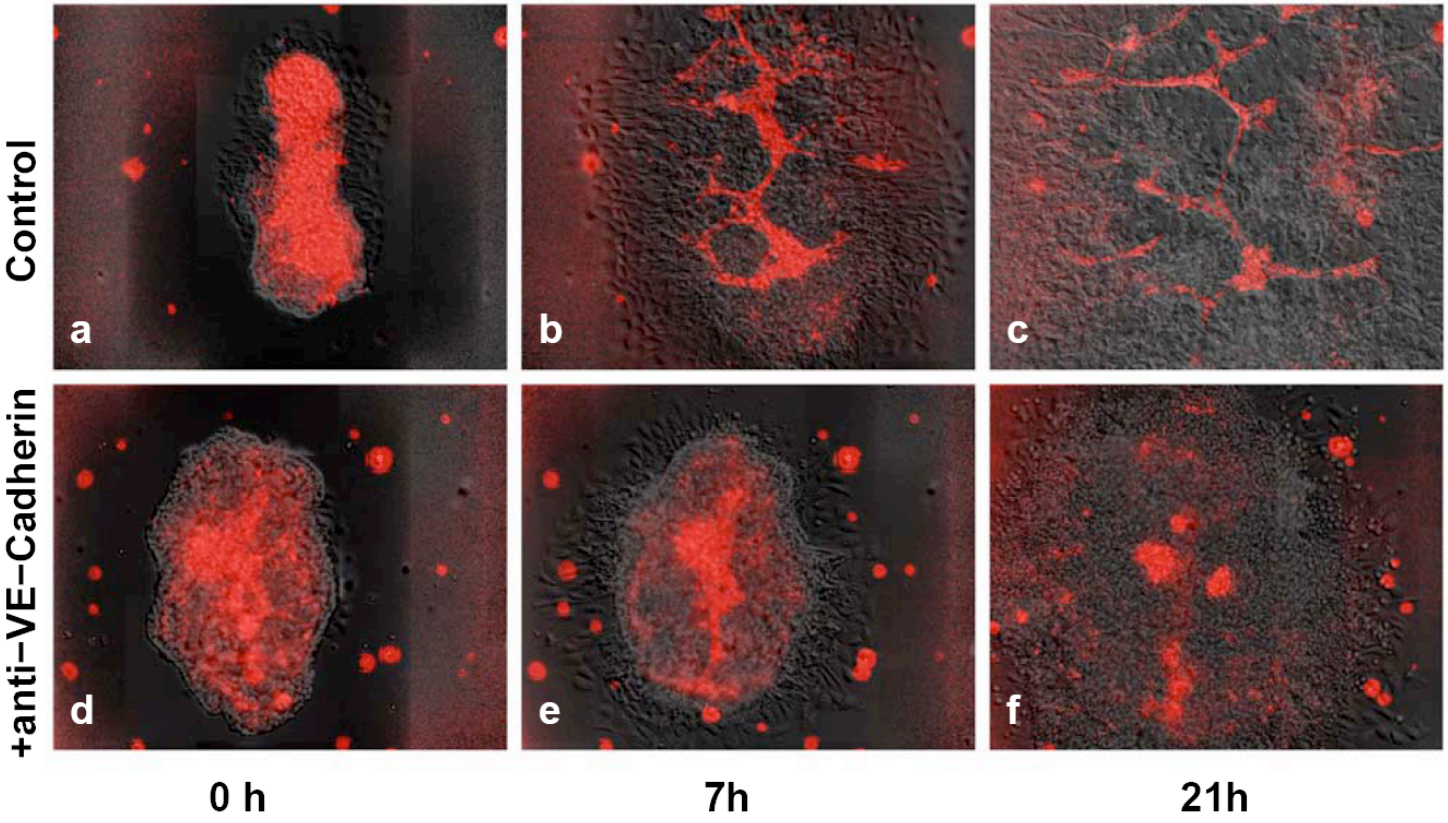
Random Separated ECs

Regular Chemotaxis Simulation



Contact-Inhibited Chemotaxis

- **VE-Cadherin** (an adhesion molecule) clusters at adherens junctions between endothelial cells and **suppresses chemotaxis** at cell-cell interfaces



Anti-VE-cadherin antibody inhibits *de novo* blood-vessel growth in mouse allantois cultures. (Roeland M. H. Merks , Erica D. Perryn , Abbas Shirinifard, and James A. Glazier, *PLoS Computational Biology* 2008)

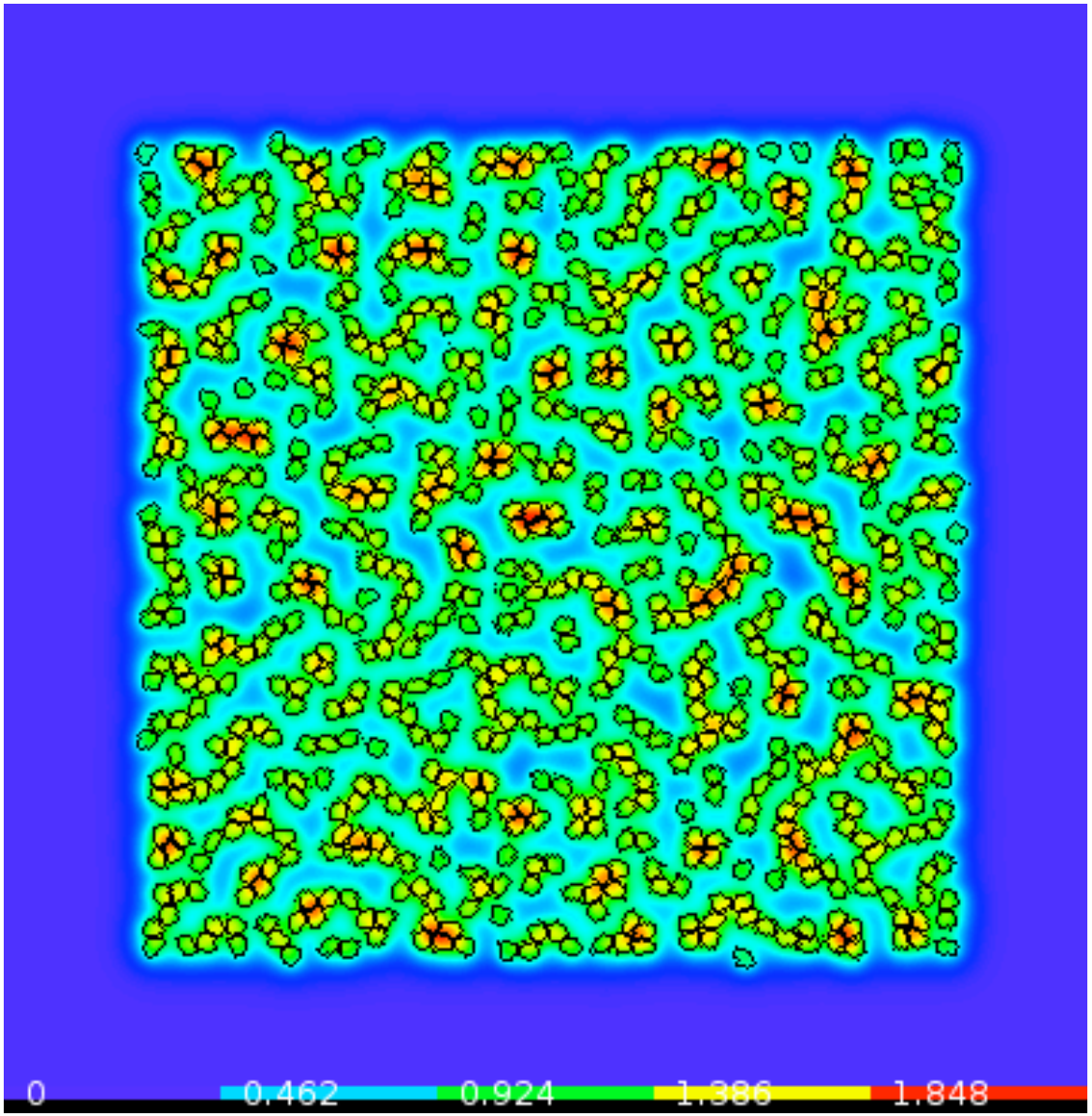
Contact Inhibition of Motility

"Context-dependent" effect of VEGF-A (Vascular-endothelial growth-factor A: stimulates vasculogenesis)

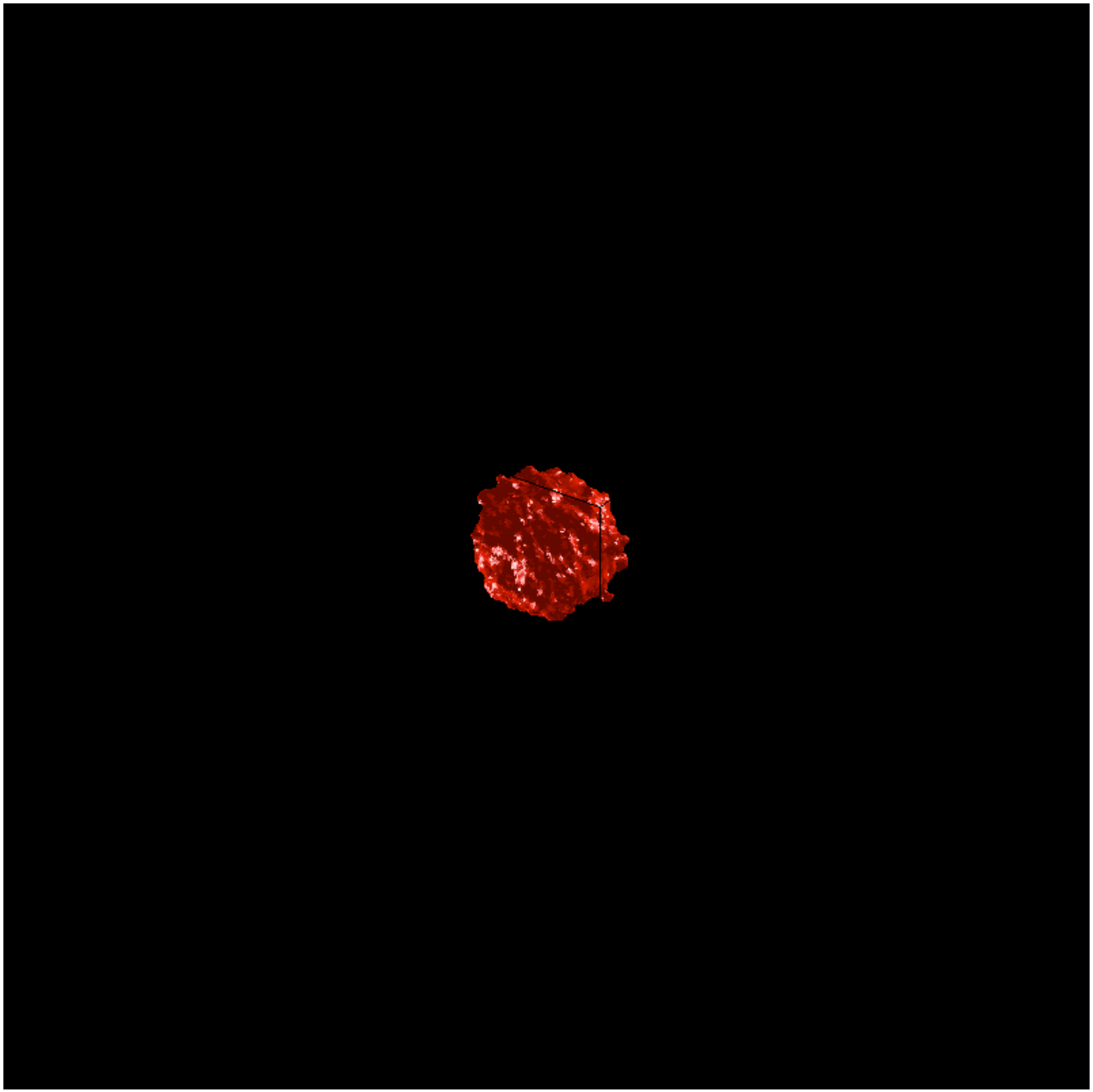
- VE-Cadherin clusters at adherens junctions between endothelial cells
- VE-Cadherin-binding → dephosporylation of VEGFR-2
- VEGF-A signaling:
  - in presence of VE-Cadherin: AKT/PKB ↑
    - cell survival
  - In absence of VE-Cadherin: ERK/MAPK ↑
    - Actin polymerization: cell motility / filopodia

In model: suppress chemotaxis at cell interfaces

Contact-Inhibited Chemotaxis Simulation



3D Vasculogenesis simulations



Simplified Vascular Tumor Growth

What is effect of Tumor-Blood Vessel adhesivity on tumor invasiveness?

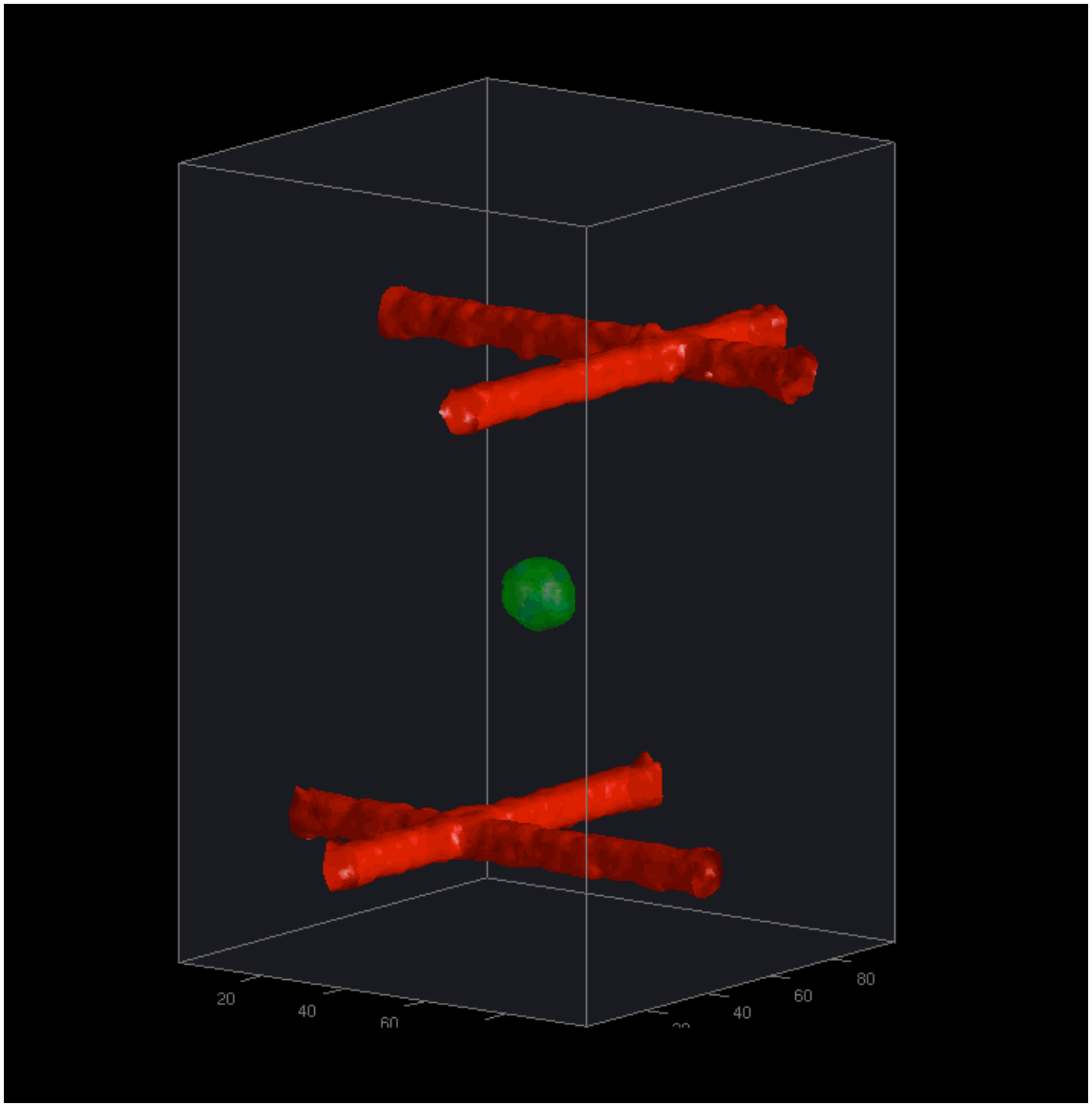
More Realistic Model:
Anderson Tumor Model.
Three-dimensional.
Diffusive Nutrient Supplied by Vasculature.
Hypoxic Tumor Cells Produce Pro-Angiogenic Factor.
Vasculature Modeled as Capillary Plexus Following our Earlier Work but Divide ECs into two classes

- Tip Cells chemotax but do not divide.
- Other ECs divide but do not chemotax.

Neglects Transport Effects in Vasculature (*e.g.* Reduction in Nutrient Supply Downstream), Variations due to Vessel Diameter, Blood Vessel Collapse, *etc*…).

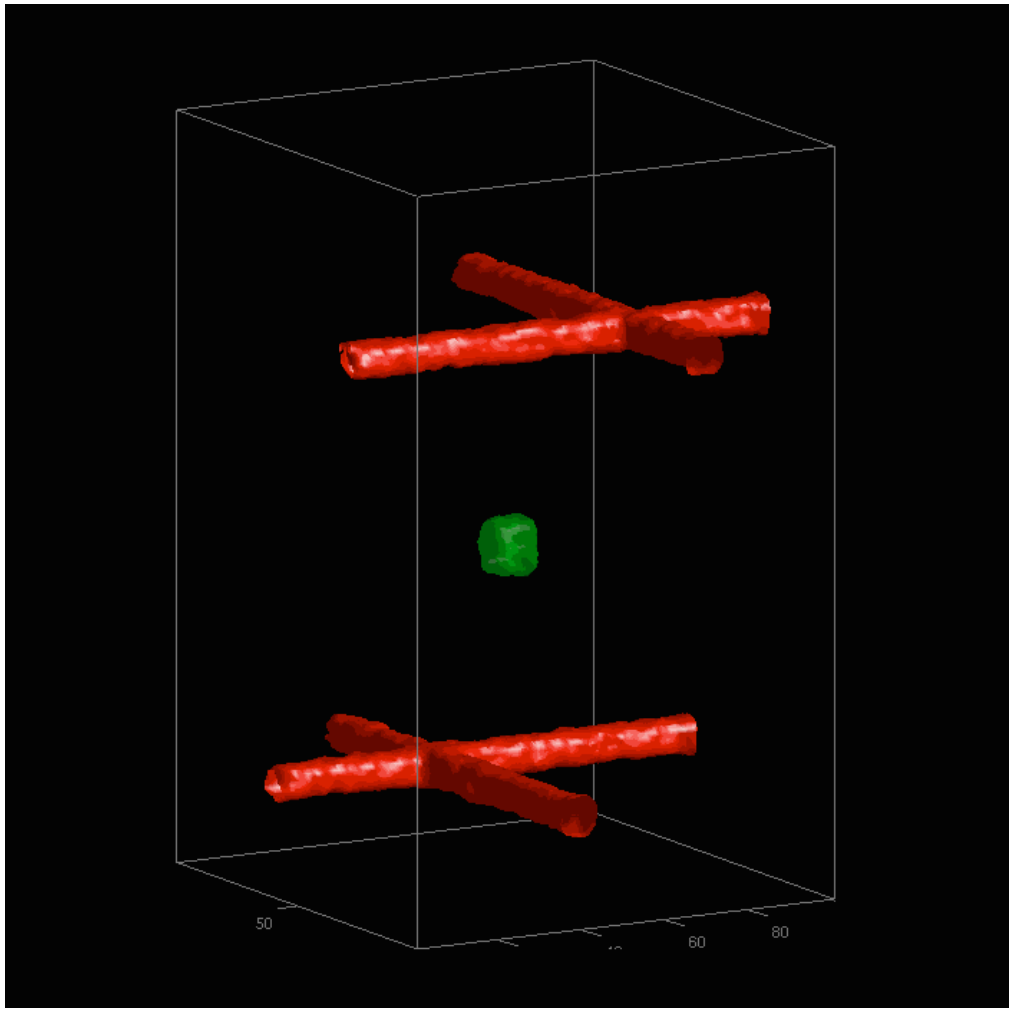
No Flow-Induced Remodeling (Easy to Add).

Tumor-Induced Vascularization (1)



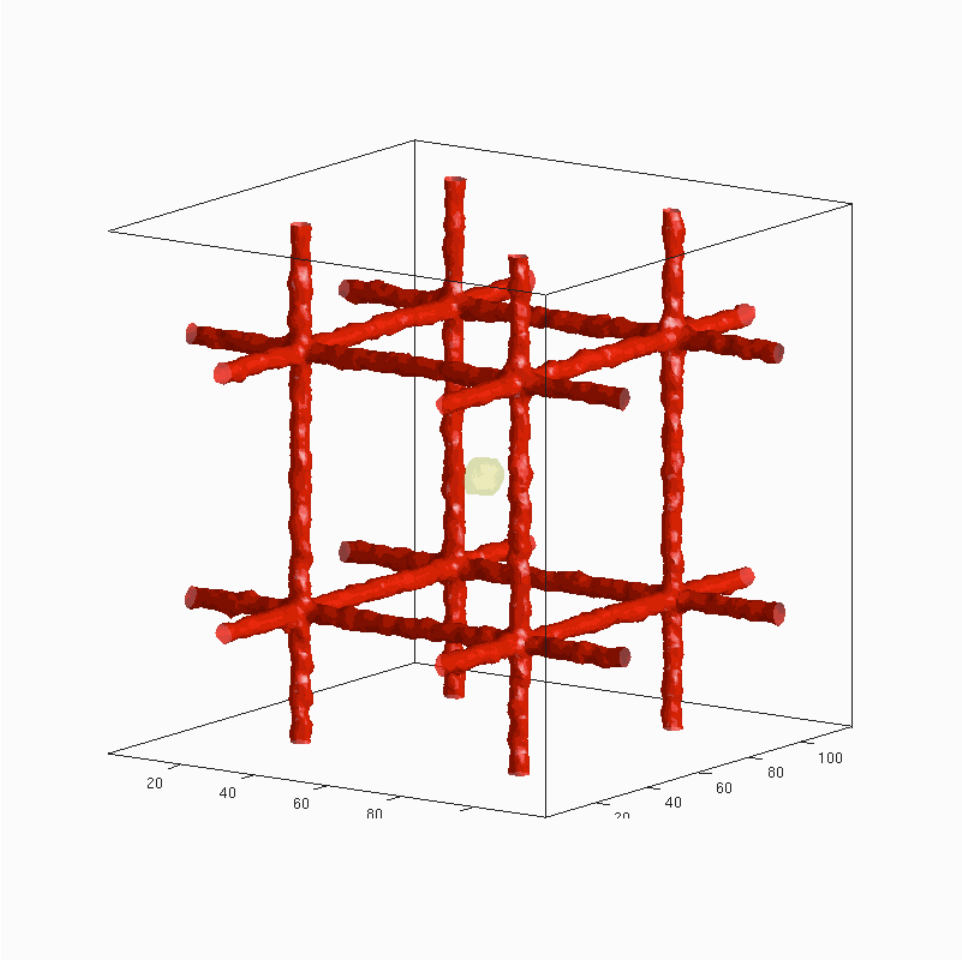
Vasculature Does Not Penetrate Tumor (*e.g.* Glioblastoma)

Tumor-Induced Vascularization (2)



Vasculature Does Penetrate Tumor

Tumor-Induced Vascularization (3)



Vasculature Does Not Penetrate Tumor

Comments and Next Steps

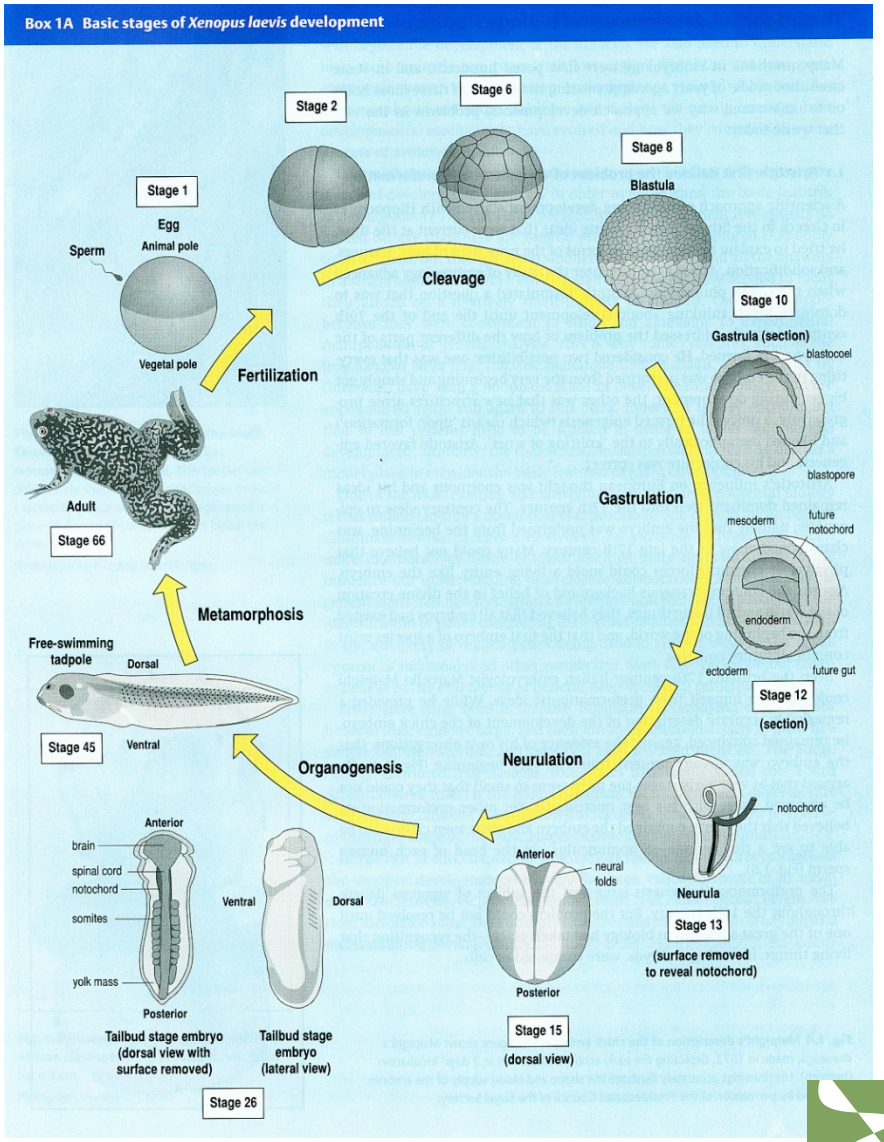
- Failure of Vasculature to Penetrate Growing Tumor can Actually Increase Tumor Invasiveness/Metastatic Potential.
- Paradox in Somatic Evolution (or Tumor as Ecosystem)—Metastatic Cells mostly Die, so Should be Selected Against.
- Implies Invasiveness Must be Selectively Advantageous but NOT because of Metastatic Potential.
- So Why?

Somatic Evolution Theory

- Tumor Environment Changes in Time (in Particular Necrotic Regions Move Around because neovascular capillaries are easily crushed by pressure due to cell growth).
- Thus cells which can move to avoid necrotic regions selected for.
- These cells **accidentally** promote Metastasis.
- We will test by including heritability variability in invasiveness and vascular collapse.

Development of Body Plan

- Specification of Body Axes
- Cleavage
- Gastrulation (Formation of Primitive Streak—Anterior-Posterior)
- Somitogenesis (Formation of AP compartments)
- Organogenesis



Gastrulation—Formation of Main Body Axis

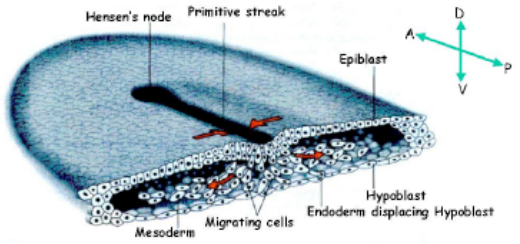
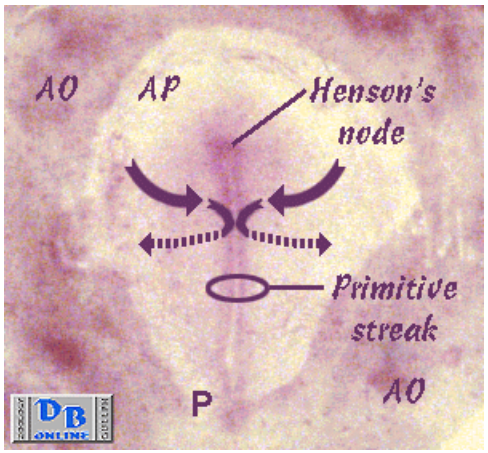
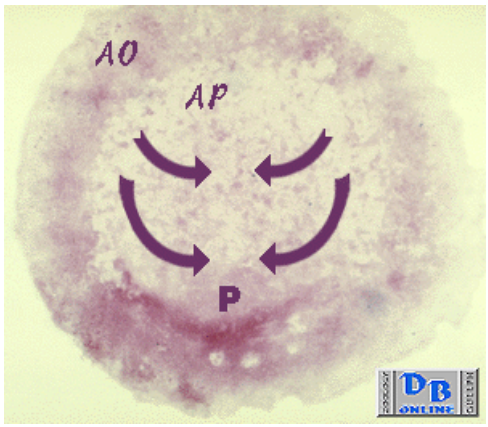
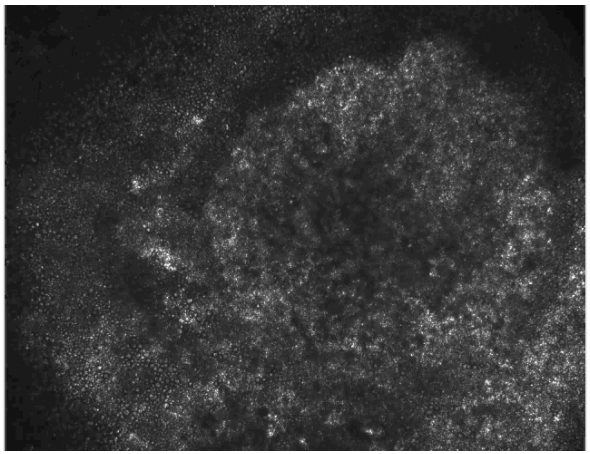
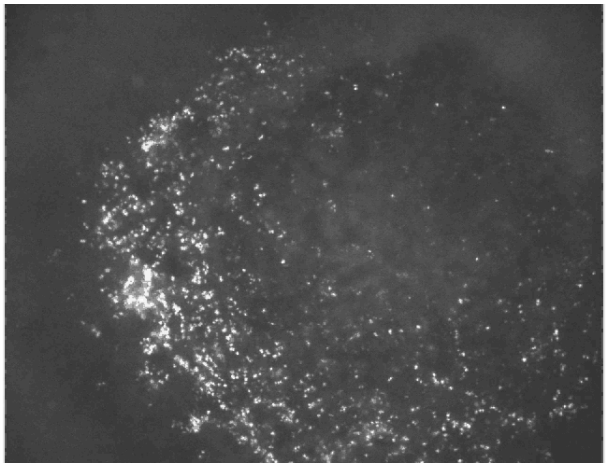


Figure 25. Formation of the primitive streak, the mesoderm and the endoderm. Adapted from [28].









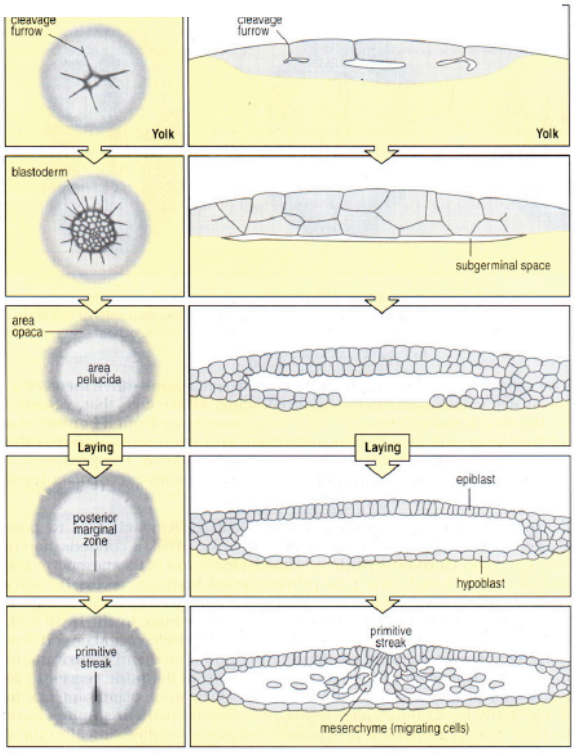
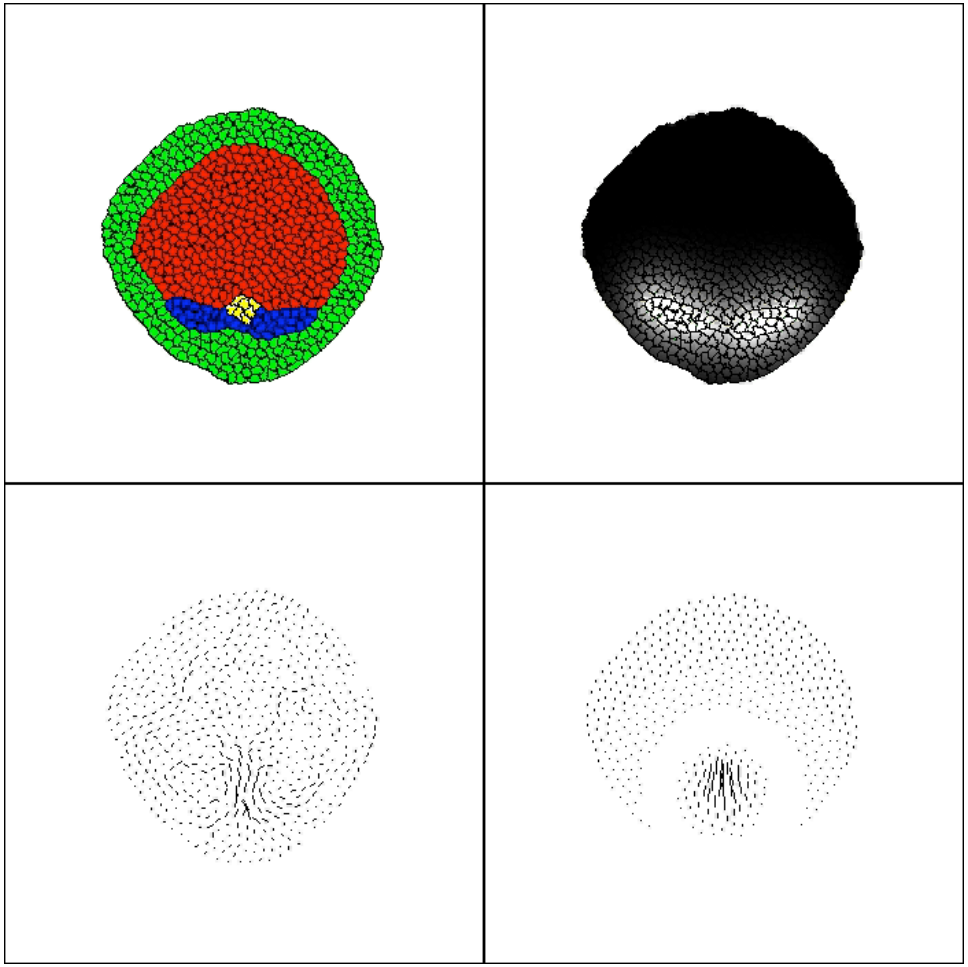
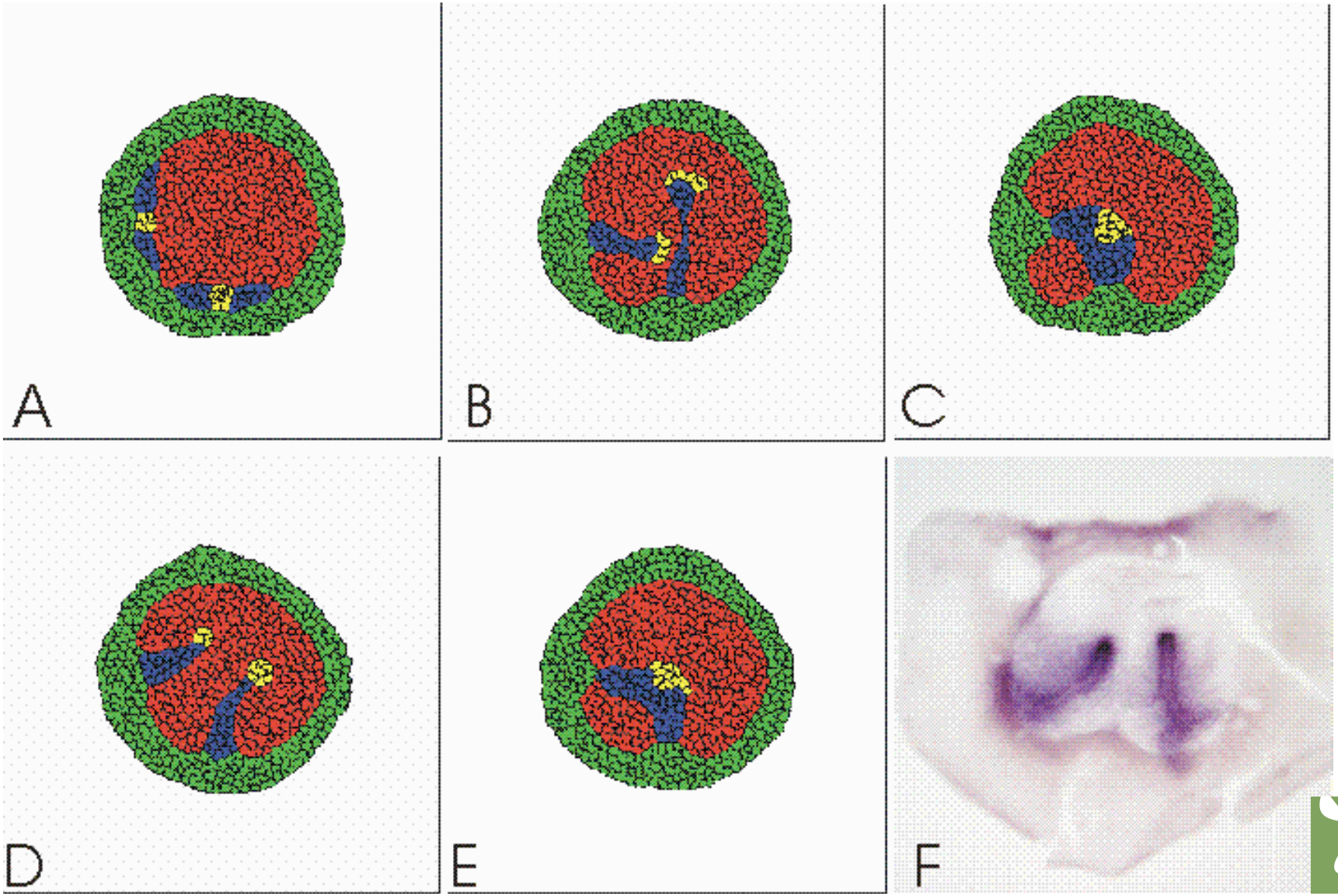


Figure 2.1: Blastoderm development in the chick embryo. Adapted from figure 2.12 in *Principles of Development, second edition* by Wolpert, 1998 [124].

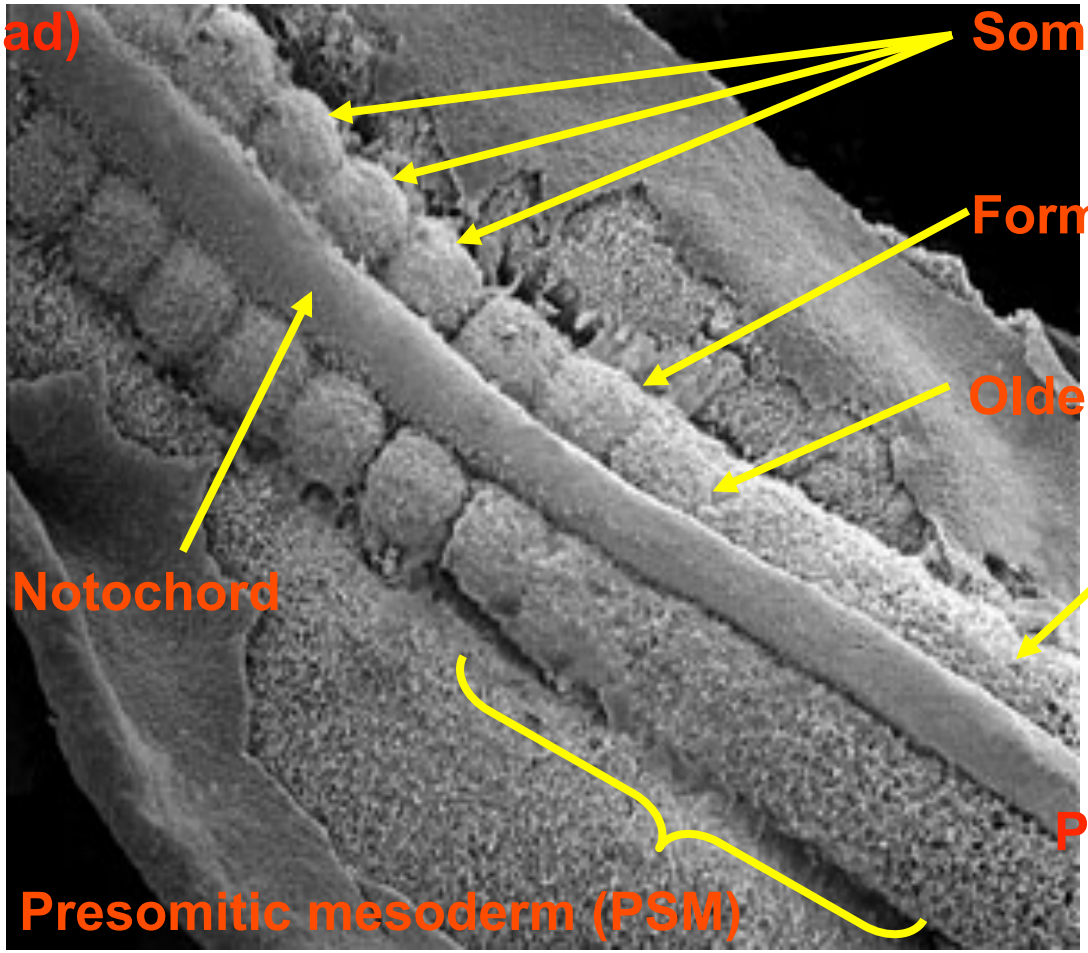
Gastrulation Model



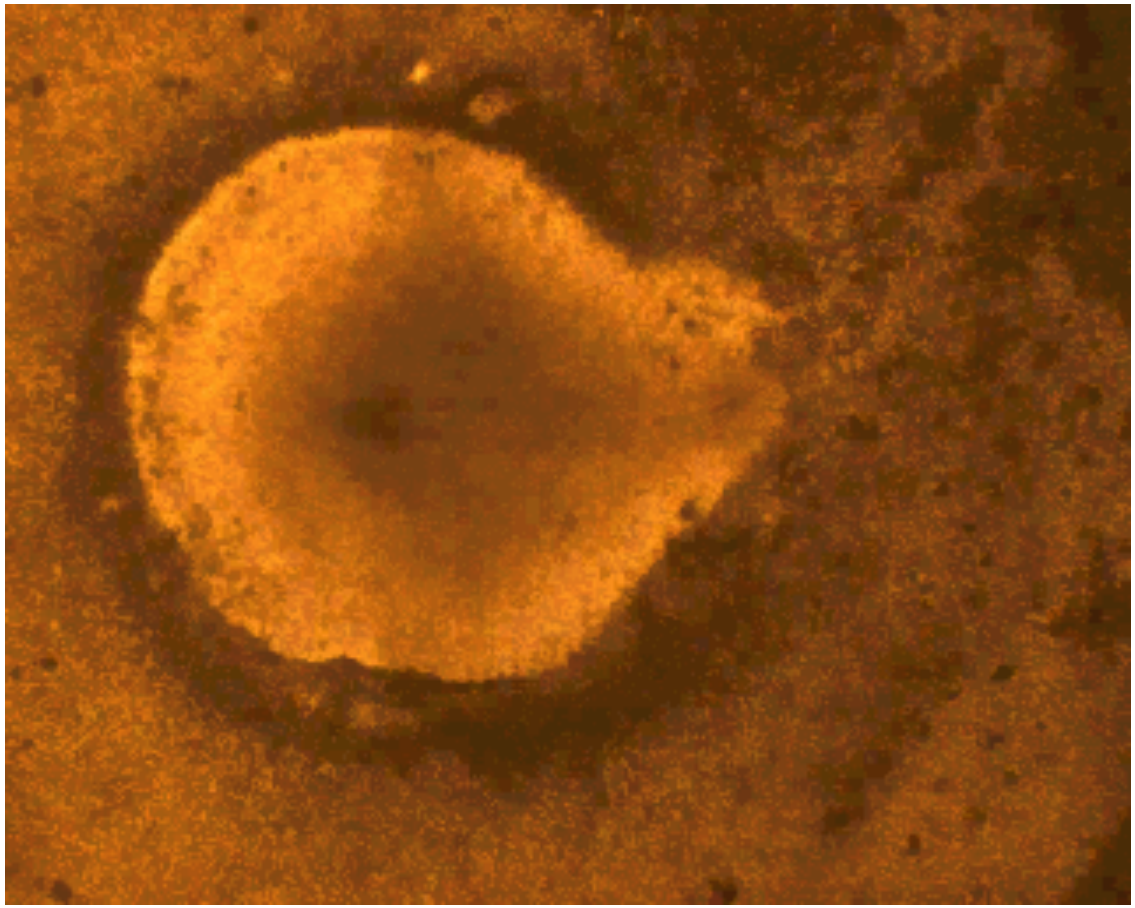
Which Chemotactic Mechanism?



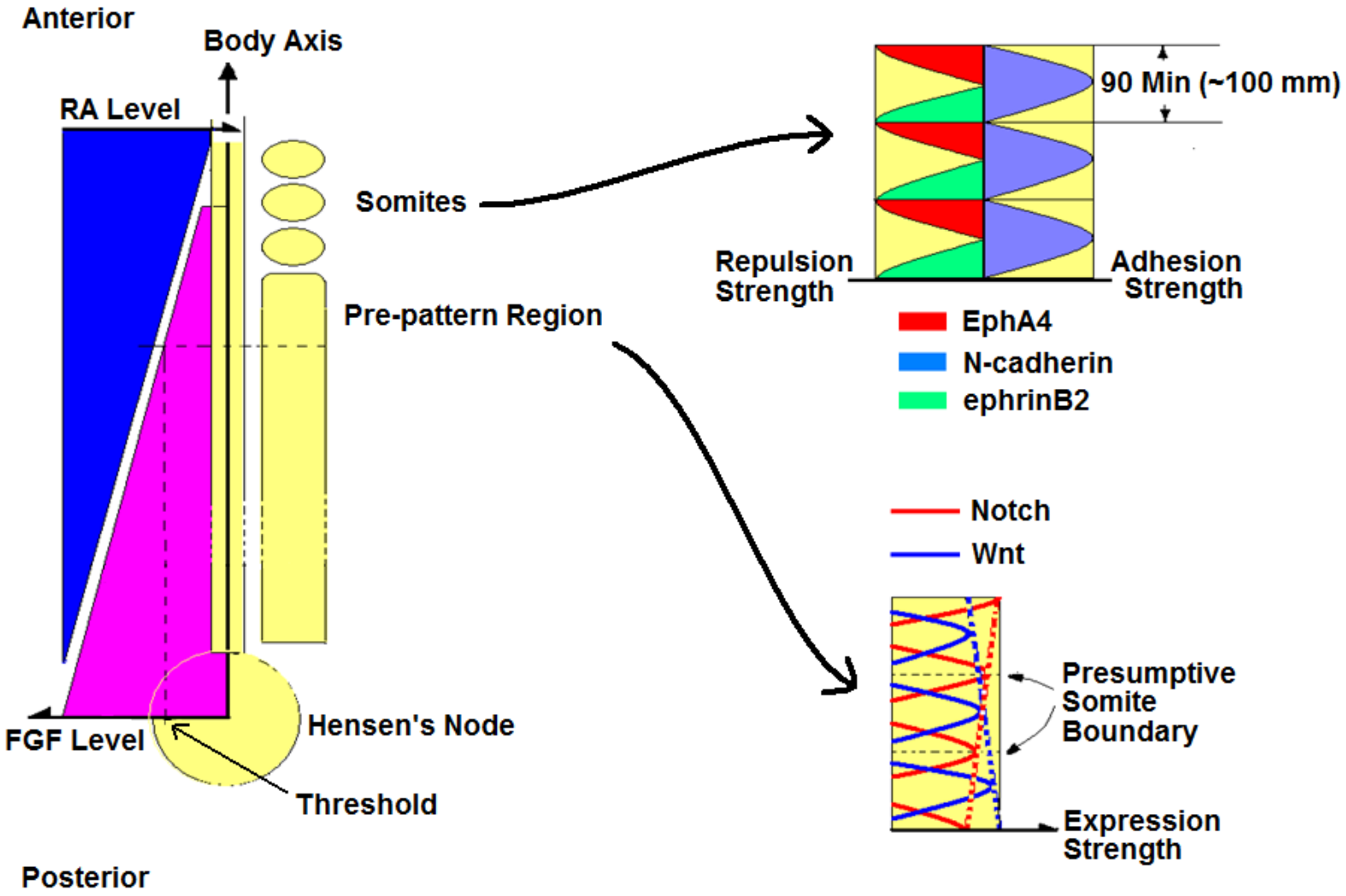
Somitogenesis



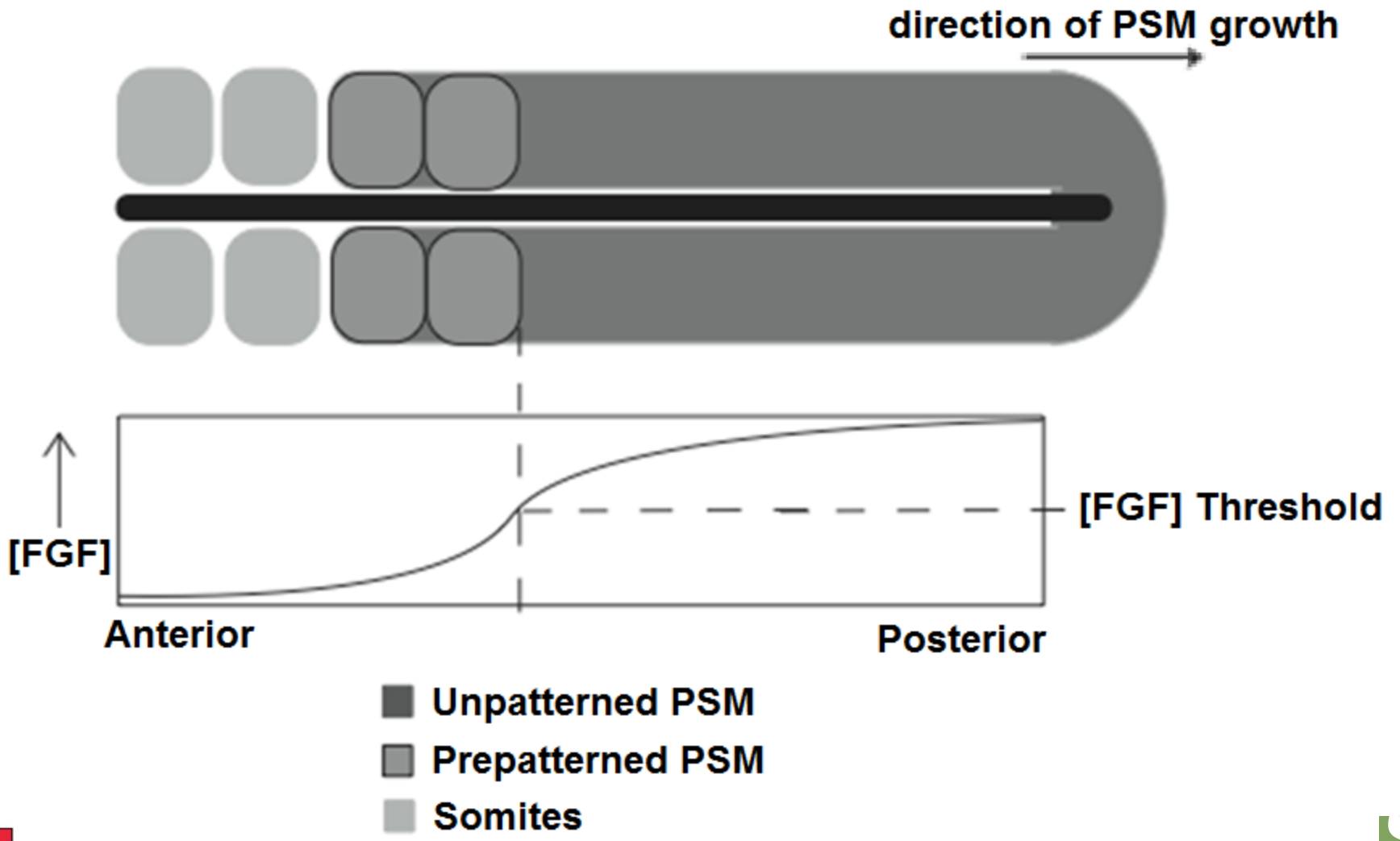
Somitogenesis

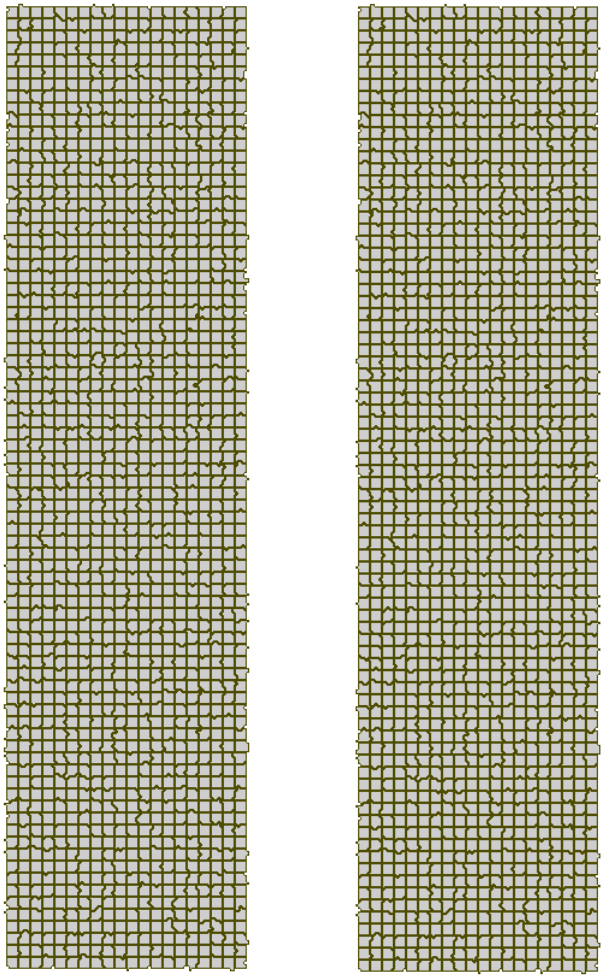


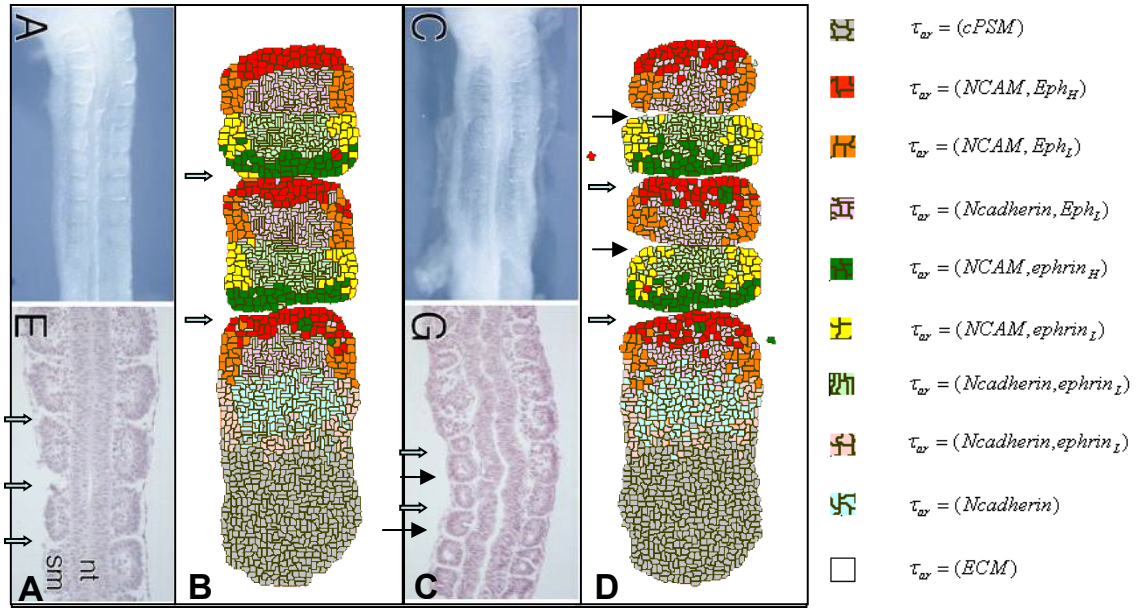
Somitogenesis



Embryo Structure

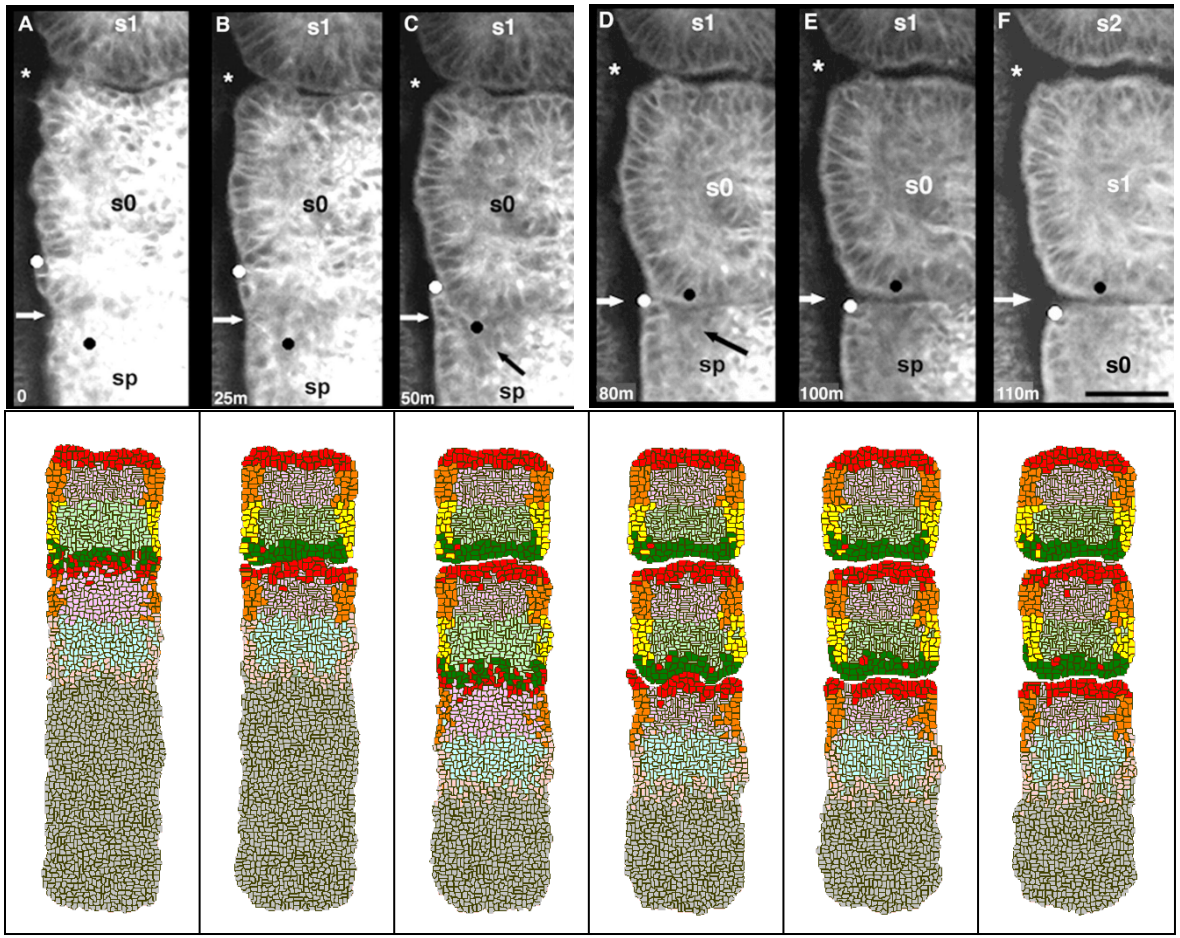






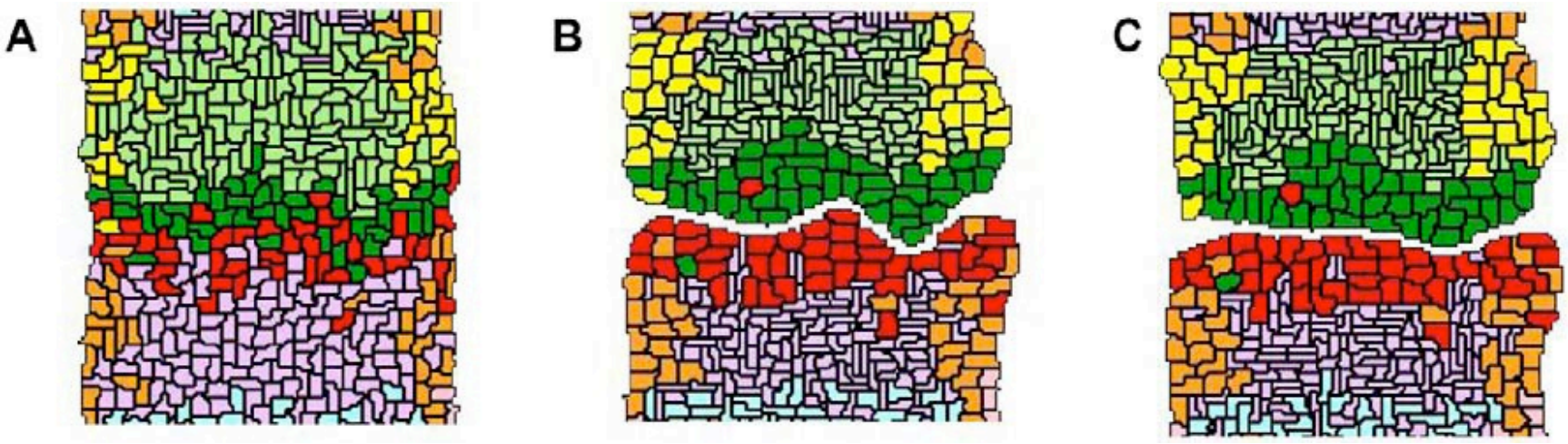
N-cadherin knockout

Compartment Boundary Crossing

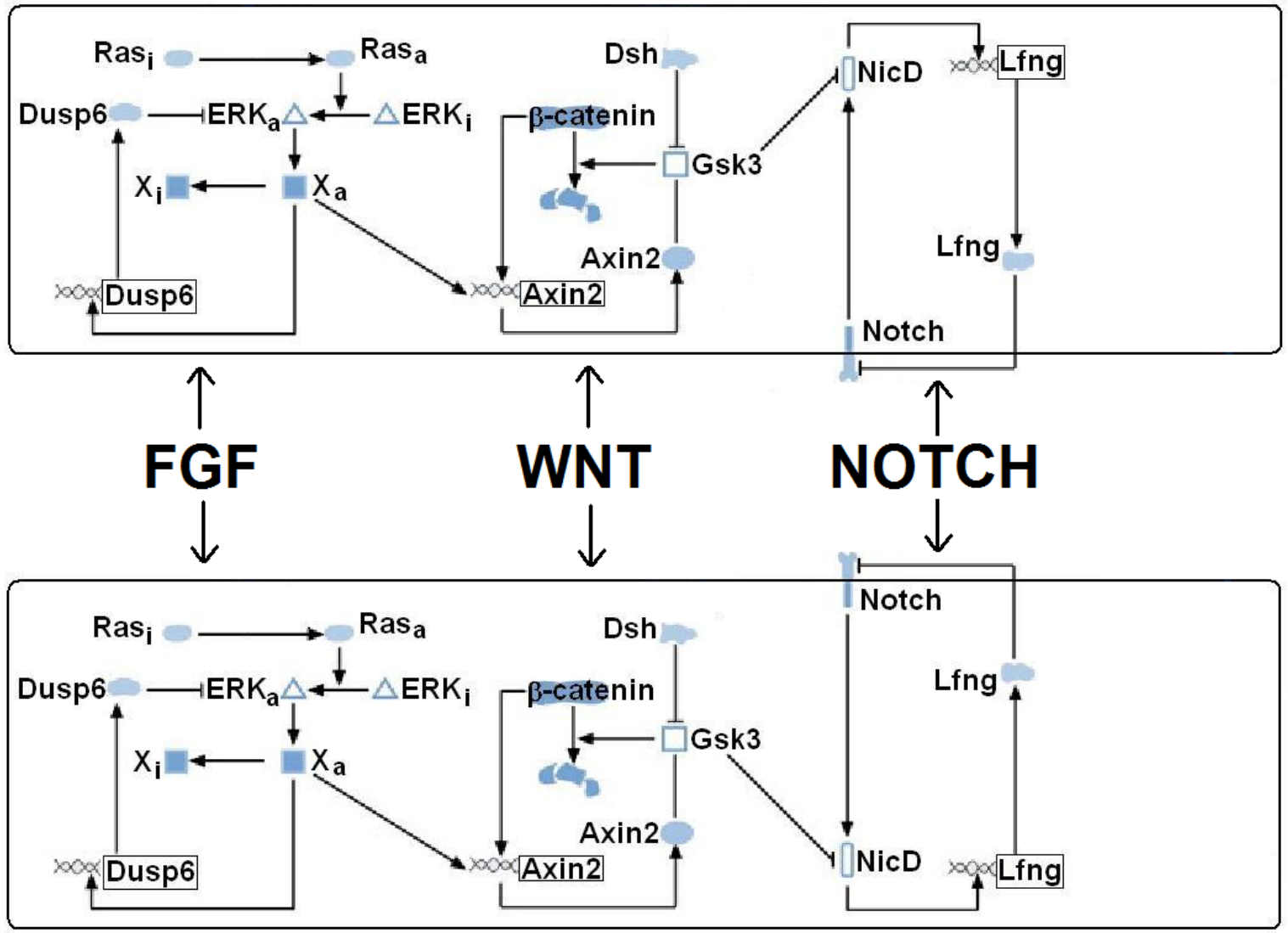


Experimental figure from Kulesa *et al.*

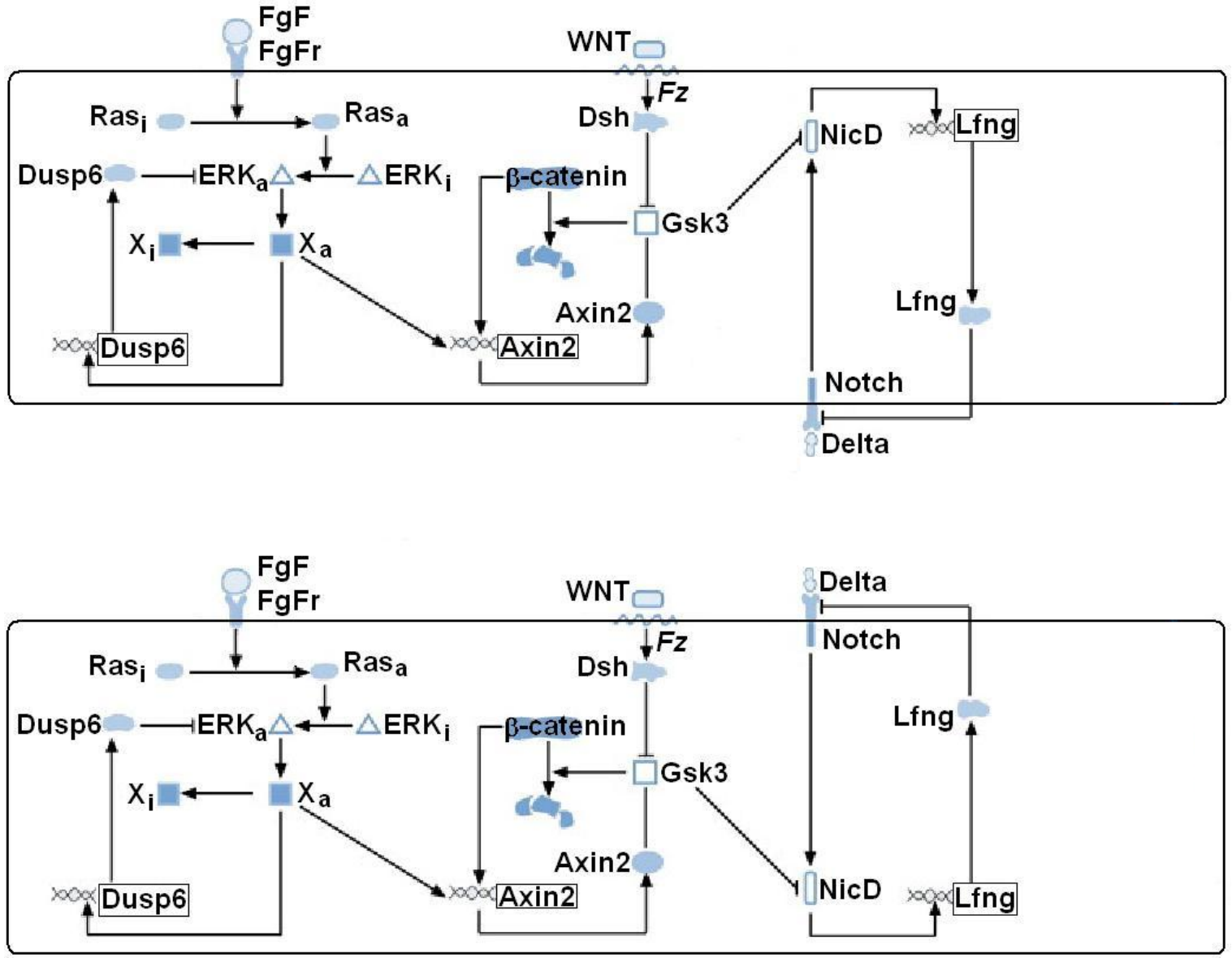
Adhesion-based Error Correction



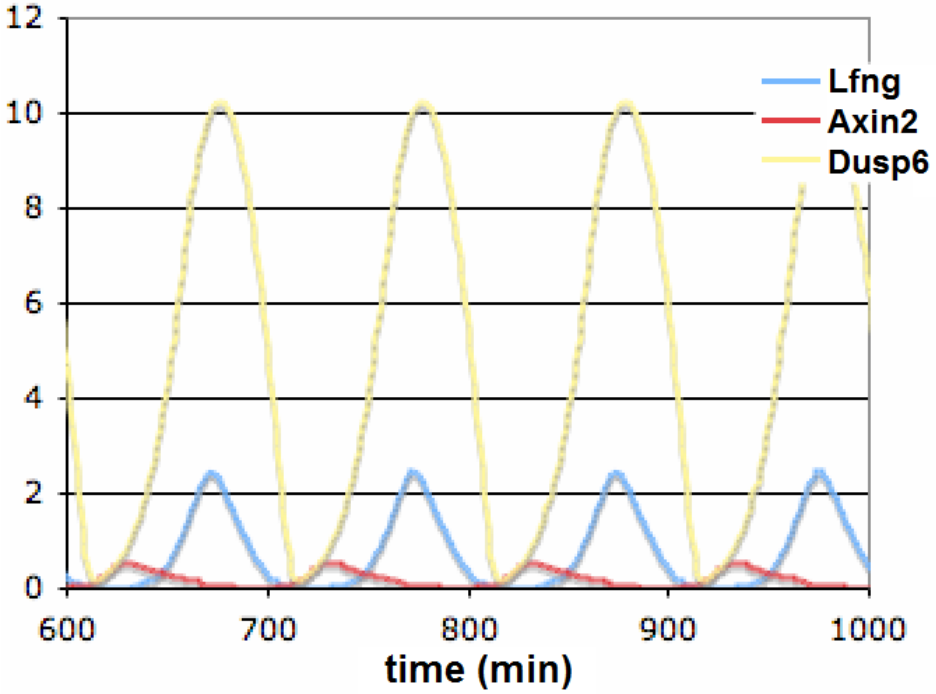
Pathways (Goldbeter & Pourquié 2008)

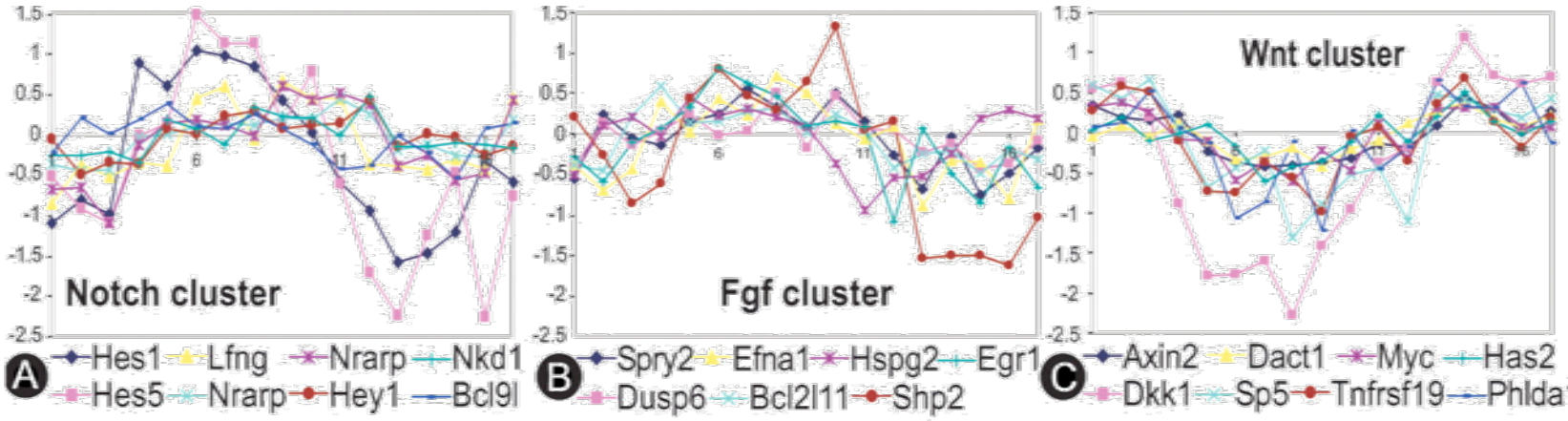


Pathways (Goldbeter & Pourquié 2008)



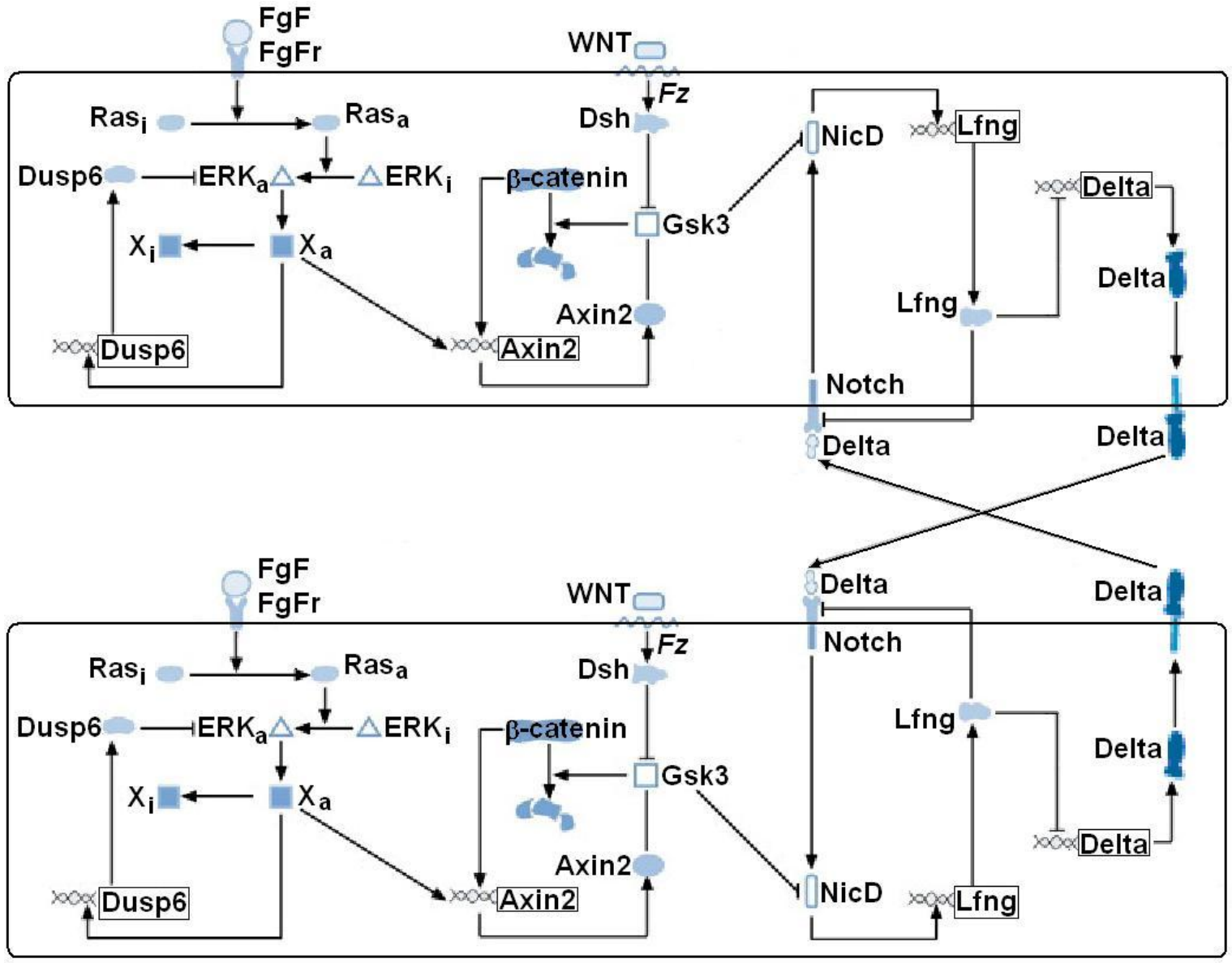
Pathways (Goldbeter & Pourquié 2008)



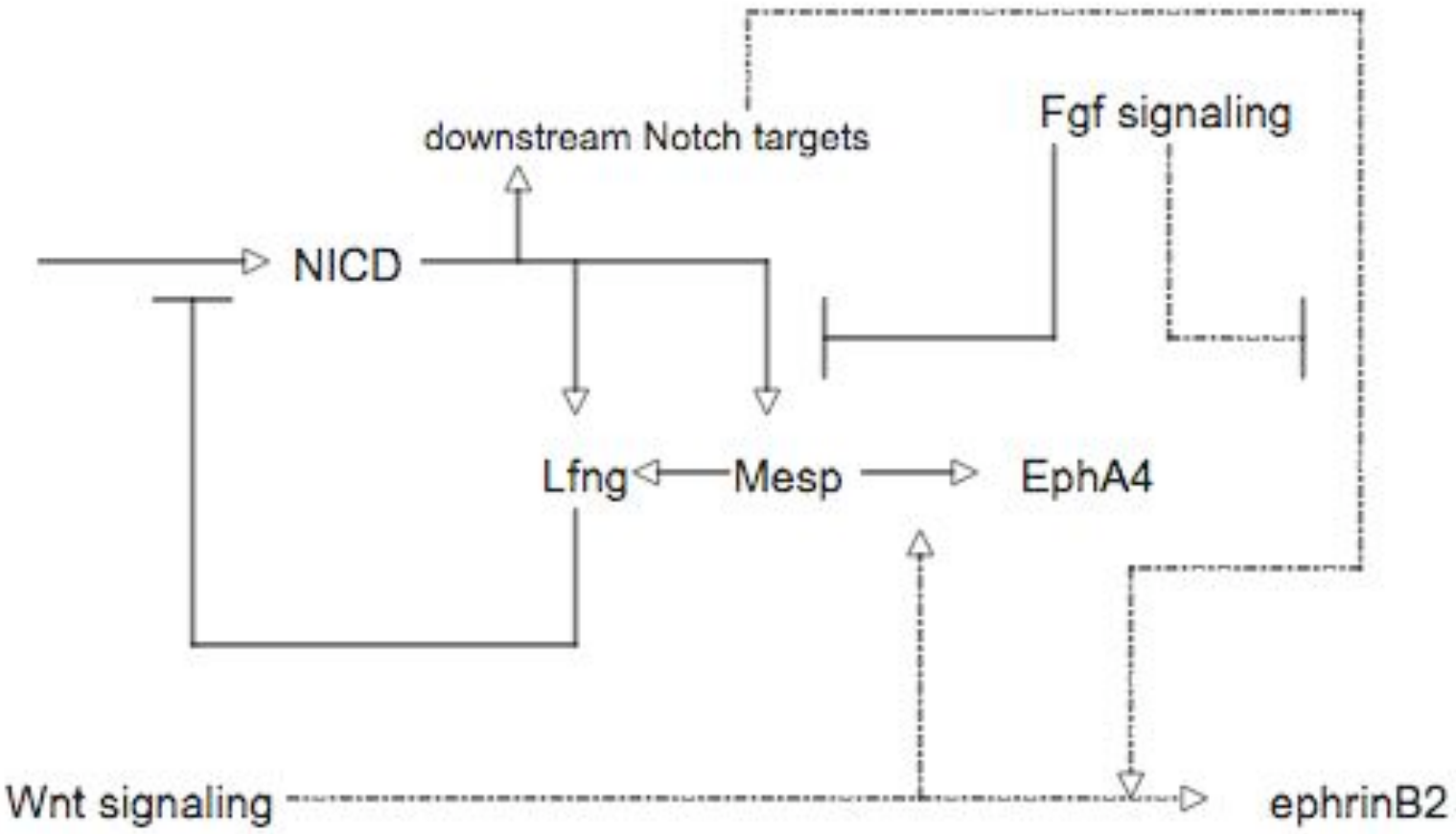


Dequeant *et al*. 2006 (microarray time series of mRNA in mouse)

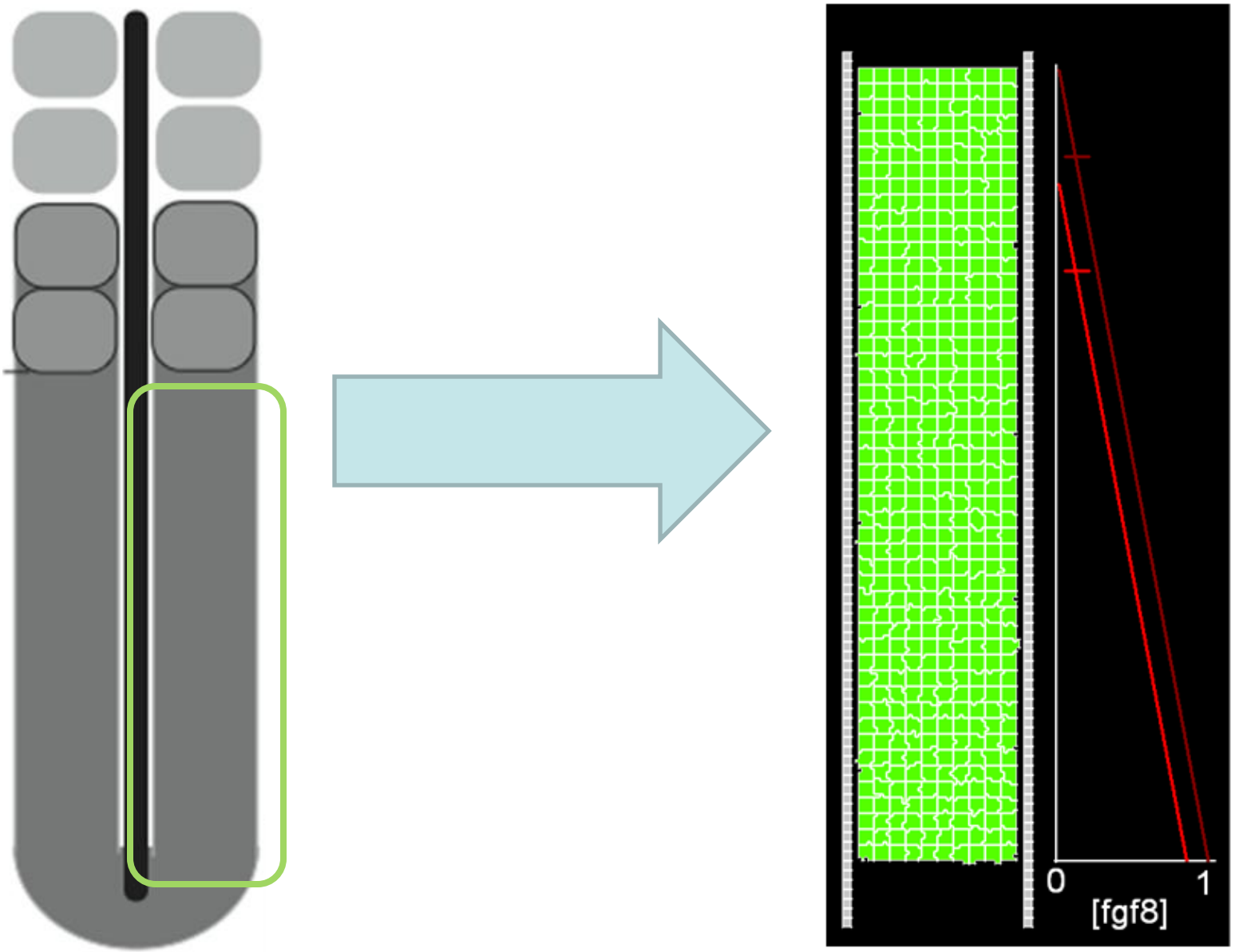
Pathways (Lewis *et al*. 2003)



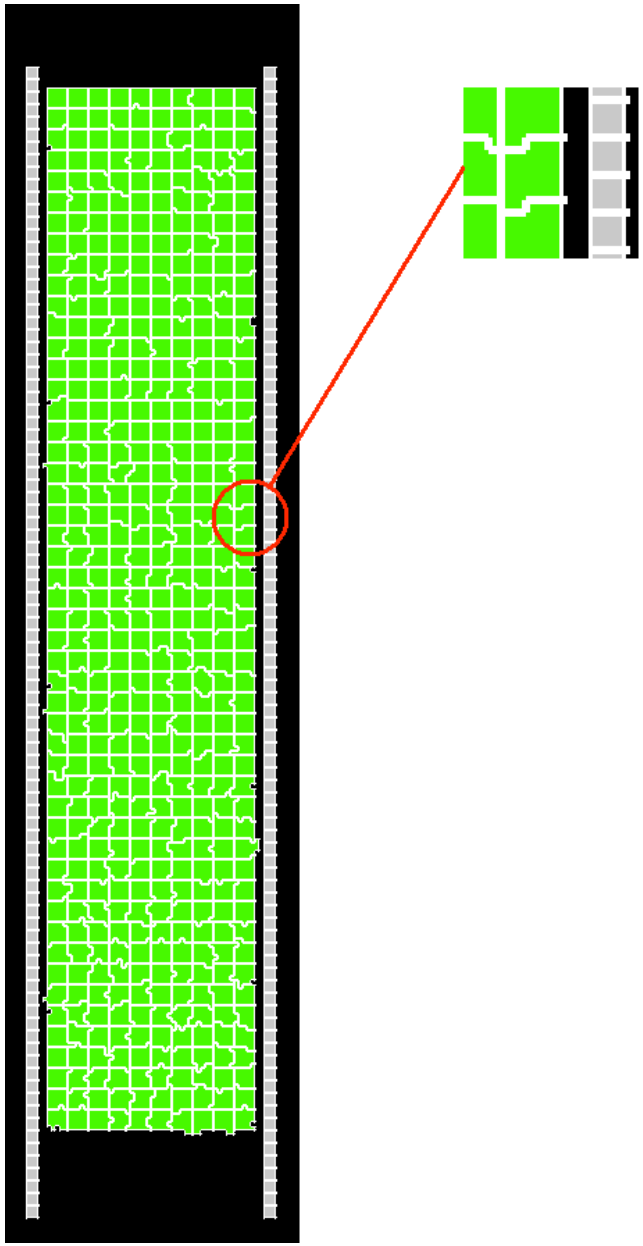
Model – Read-Out Mechanism



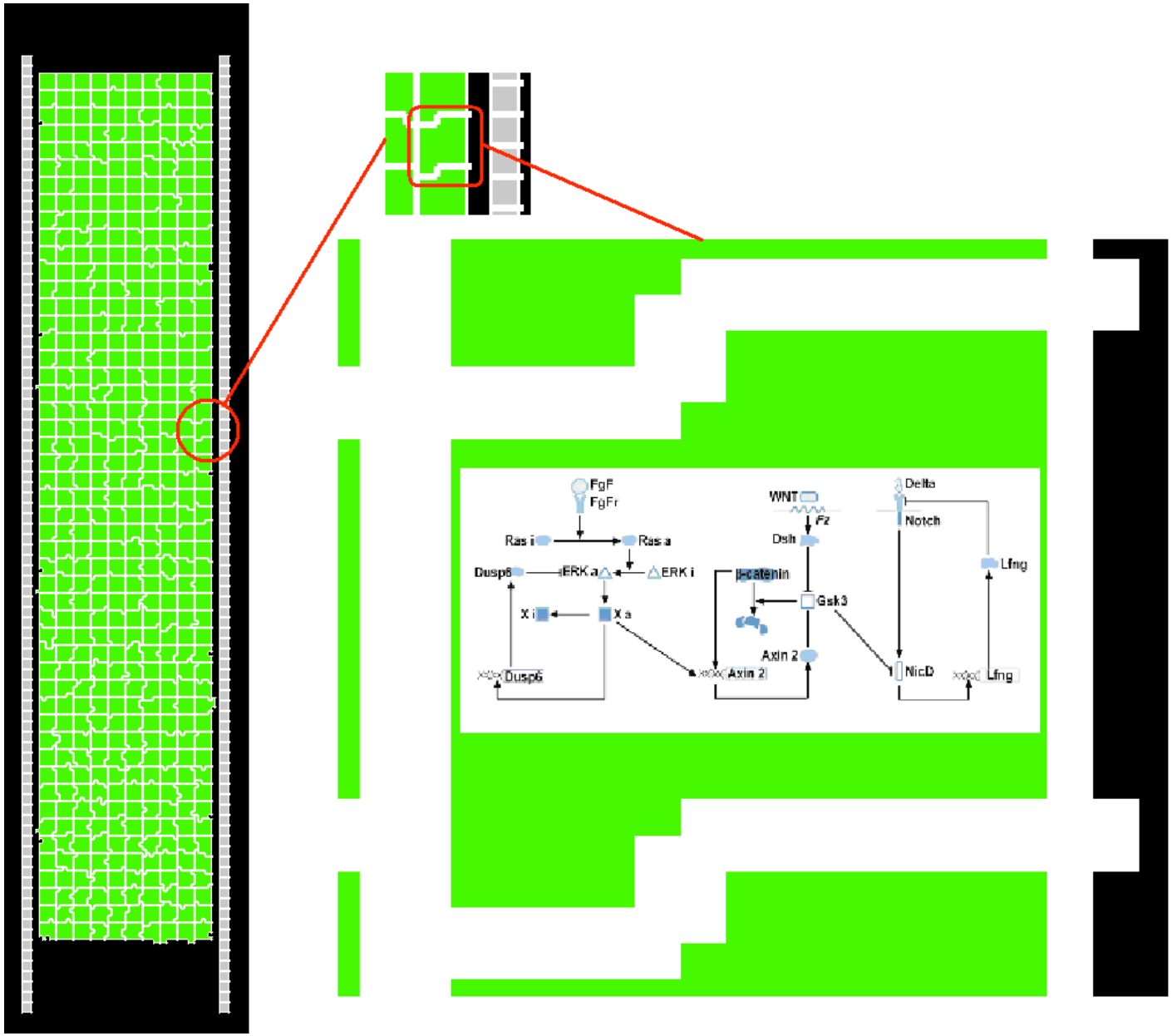
Model - PSM



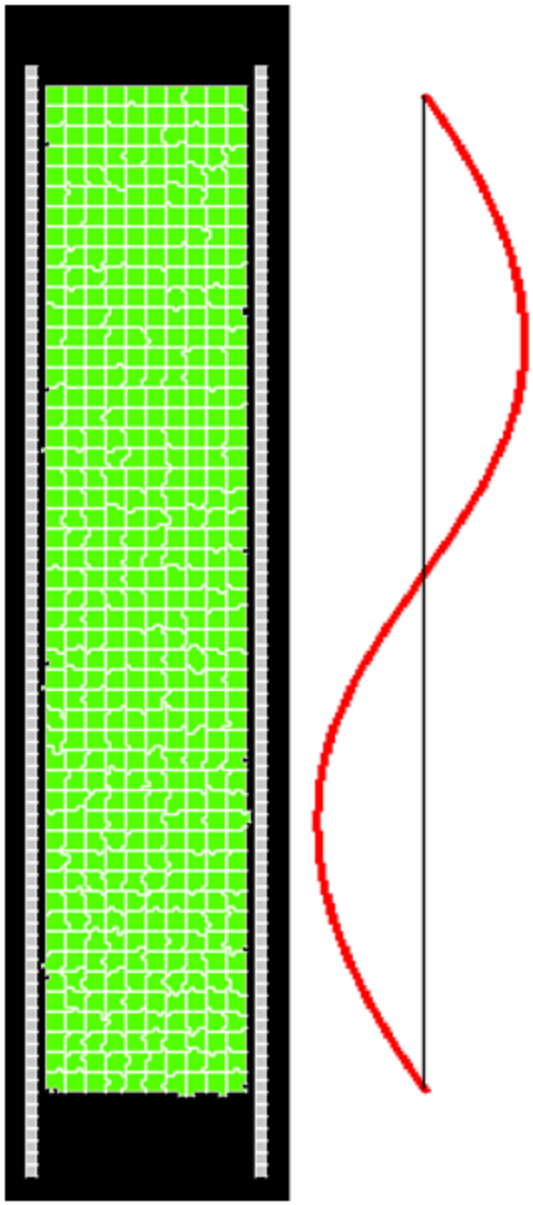
Model - Clock



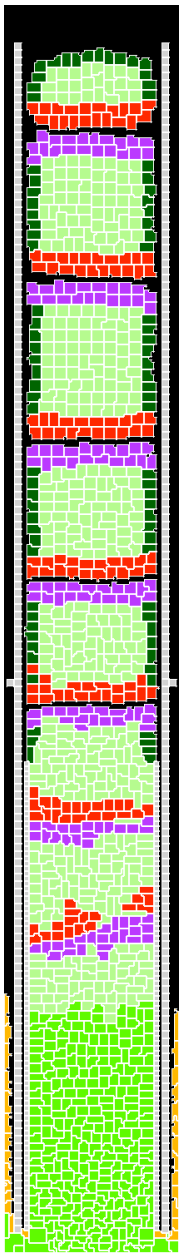
Model - Clock


FgF
FgFr
Ras i
Ras a
Dusp6
ERK a
ERK i
X i
X a
Dusp6
WNT
Fz
Dsh
β-catenin
Gsk3
Axin 2
Axin 2
Delta
Notch
Lfng
NicD
Lfng

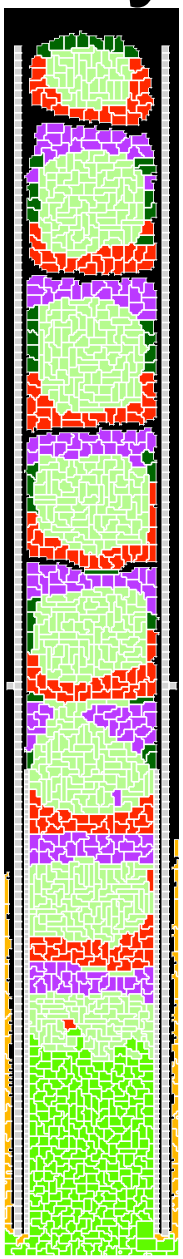
Model – Initial Conditions



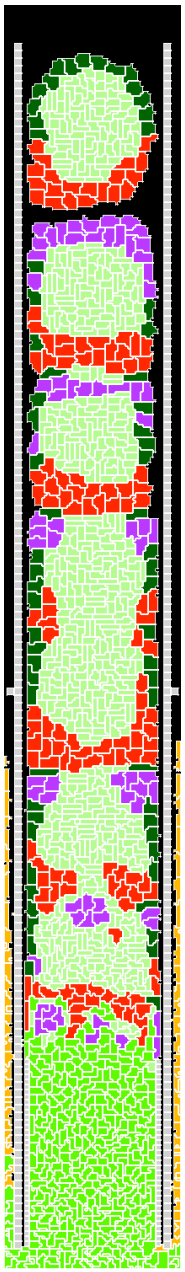
Preliminary Results



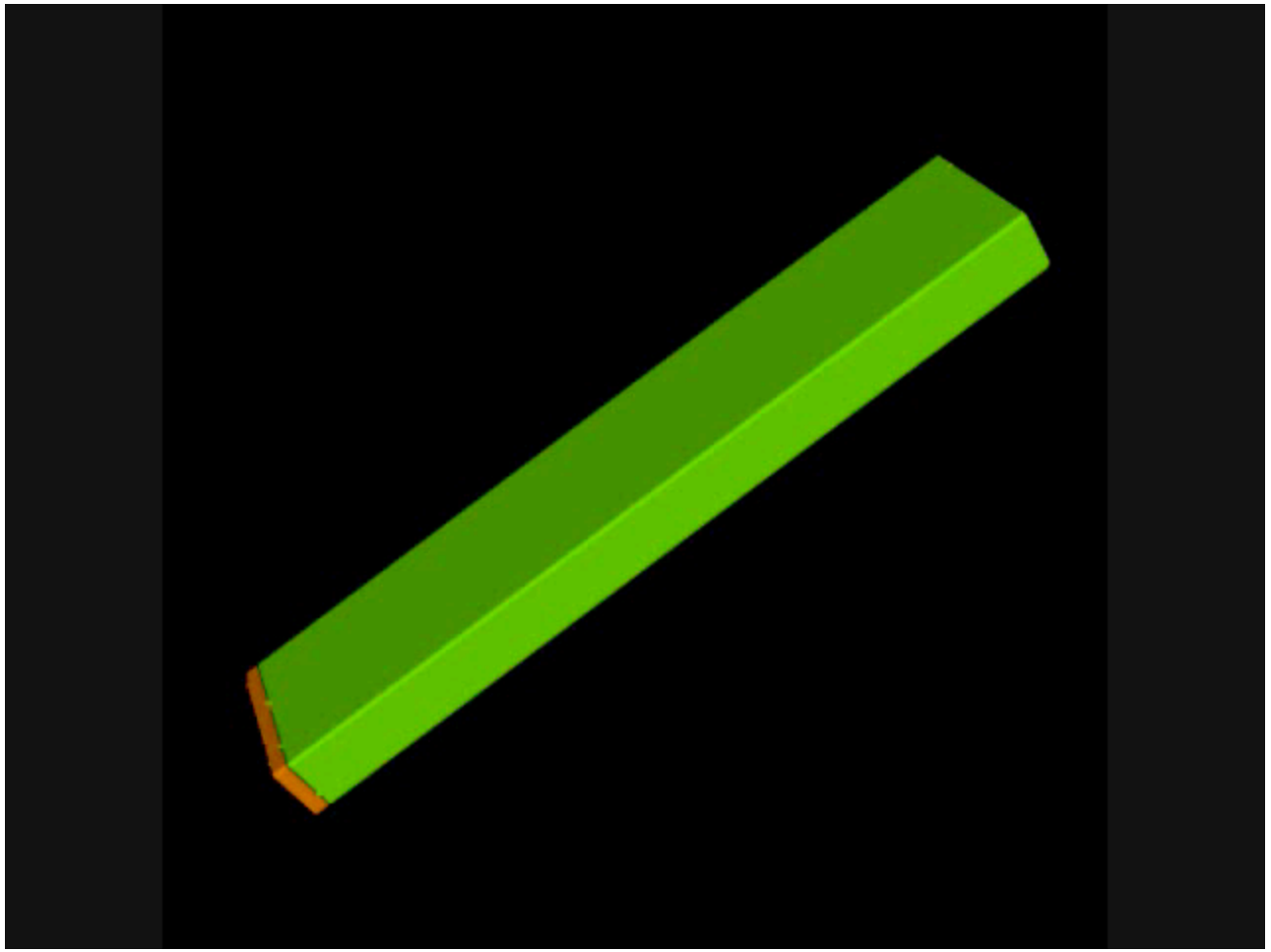
More Stiff



More Loose



3D Version



Conclusions (I)

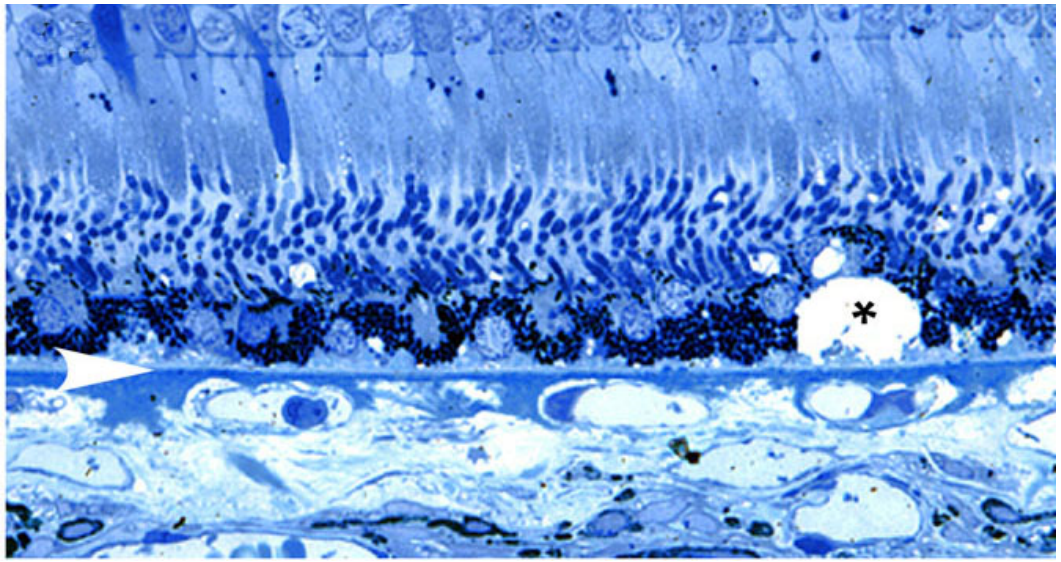
- Observed Patterns of N-CAM, N-Cadherin, EphA4 and ephrinB2 suffice to explain observed somite morphology development.
- Simulations illustrate a new mechanism of error correction.
- Goldbeter-Pourquie and Lewis models can combine with adhesion to create observed patterns only if cells in central PSM zone are weakly motile.
- Segmentation more robust in 3D than in 2D approximation.

Conclusions (II)

- Need pathways connecting somitic clock to adhesion, motility and cell cycle.
- Need experimental measurements of cell motility.
- Need better data on tissue mechanics at micro level.

Age-Related Macular Degeneration

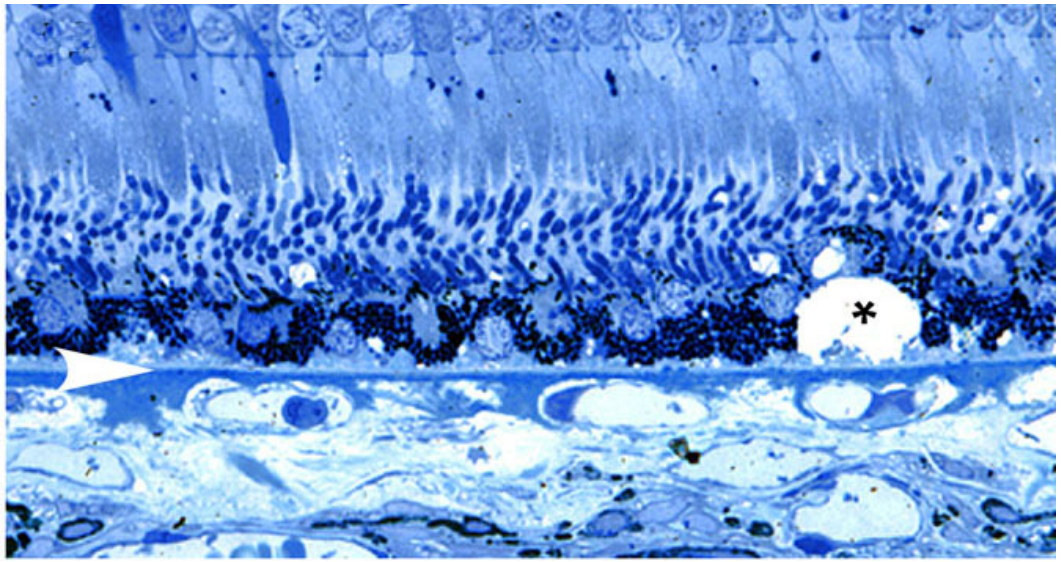
- The receptor cells in the retina have one of the highest metabolic rates in the body.
- Most nutrient and oxygen supplied from behind the retina by the choroid plexus.
- Plexus Separated from Retina by Bruch's Membrane.



http://webvision.med.utah.edu/imageswv/Hagerman.Fig15.jpg

Age-Related Macular Degeneration

- Deposition of waste between retinal cells and Bruch's membrane can lead to hypertrophy of vasculature.
- Causes deterioration of vision.
- In extreme cases can cause blindness.
- Mechanism and treatment strategy poorly understood.



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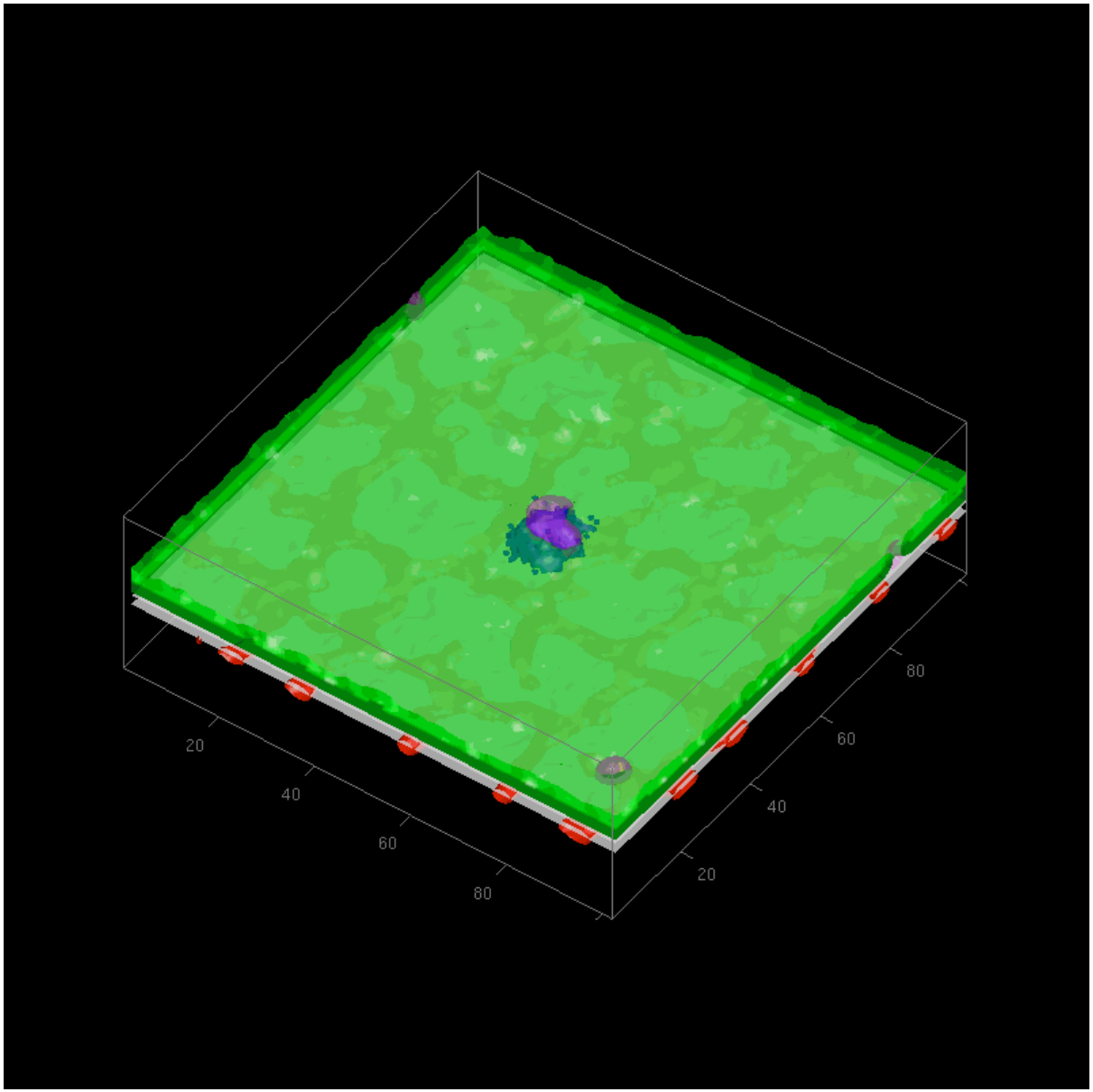

Comments (1)

- CompuCell3D is a General Modeling Framework. Can Combine with Other Simulation Methods.
- Easy to Add Detailed Subcell Models of Pathways, Metabolism…
- Easy to Add Cell Variability, Stem-like Cells…
- Run on Single Laptop.

- Happy to Help Integrate this Method with Your Own Continuum or Subcellular Methods.

Comments (2)

- Lack of Right Kind of Experimental Data:
  - Cell Tracking.
  - Adhesivity Measures.
  - Relationship between *e.g.* cell-surface cadherin densities and adhesion energies/unit area.
  - Tissue Mechanics.
  - Readout Mechanisms connecting Signals→Adhesion and Adhesion→Cell Cycle.

Needs

- Implementation-Independent Cell Behavior Phenomenology Ontology/ML (*e.g.* definitions of “mitosis,” “chemotaxis,”…).
- Standard Linkages to other Packages (*e.g.* Physiome).
- Improved Units Definition.
- Model Validation Tools.
- MPI Support?

CompuCell3D Allows You Easily to Reproduce the Models in this Talk, and Develop Your Own

- **CompuCell3D Training Workshop August 17-21, 2009, in Bloomington Indiana, USA (some funding available).**
- **Looking for new collaborations.**
- **Can support training of people interested in learning to use or enhance CompuCell3D to build specific models.**
- **Looking for collaborations on Ontology/ML development.**
- **Looking for collaborations on Package Interoperabilty.**
- **Hiring Computer Simulation-Oriented Postdoc to Help Develop CC3D.**

If You Want to Learn More

Please Visit Our Web Location at http://www.compucell3d.org and Try Downloading it Yourself!

CompuCell3D Collaboration

University of Notre Dame, Indiana University, Kansas University Medical Center

People: Mark Alber, Ariel Balter, Julio Belmonte, Rajiv Chaturvedi, Nan Chen, Trevor Cickovski, Jeff Coffland, Michael Crocker, Rita deAlmeida, Gabor Forgacs, Tilmann Glimm, Francois Graner, Randy Heiland, George Hentschel, Susan Hester, Chengbang Huang, Jesus Izaguirre, Yi Jiang, Charles Little, Roeland Merks, Charles Moad, Chris Mueller, Stuart Newman, Nikodem Poplawski, Herbert Sauro, Abbas Shirinifard, Andy Somogyi, Maciej Swat, Gilberto Thomas, Benjamin Zaitlen

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Websites:

http://www.biocomplexity.indiana.edu

http://www.compucell3d.org

Google keyword: CompuCell3D

•CompuCell3D Training Workshop August 17-21, 2009.

•Hiring (4+) Postdocs: (2) Computer Simulation-Oriented to Help Develop CC3D. (1) Ontologist, (1) Experimentalist.